

# Lymphom Kompetenz KOMPAKT



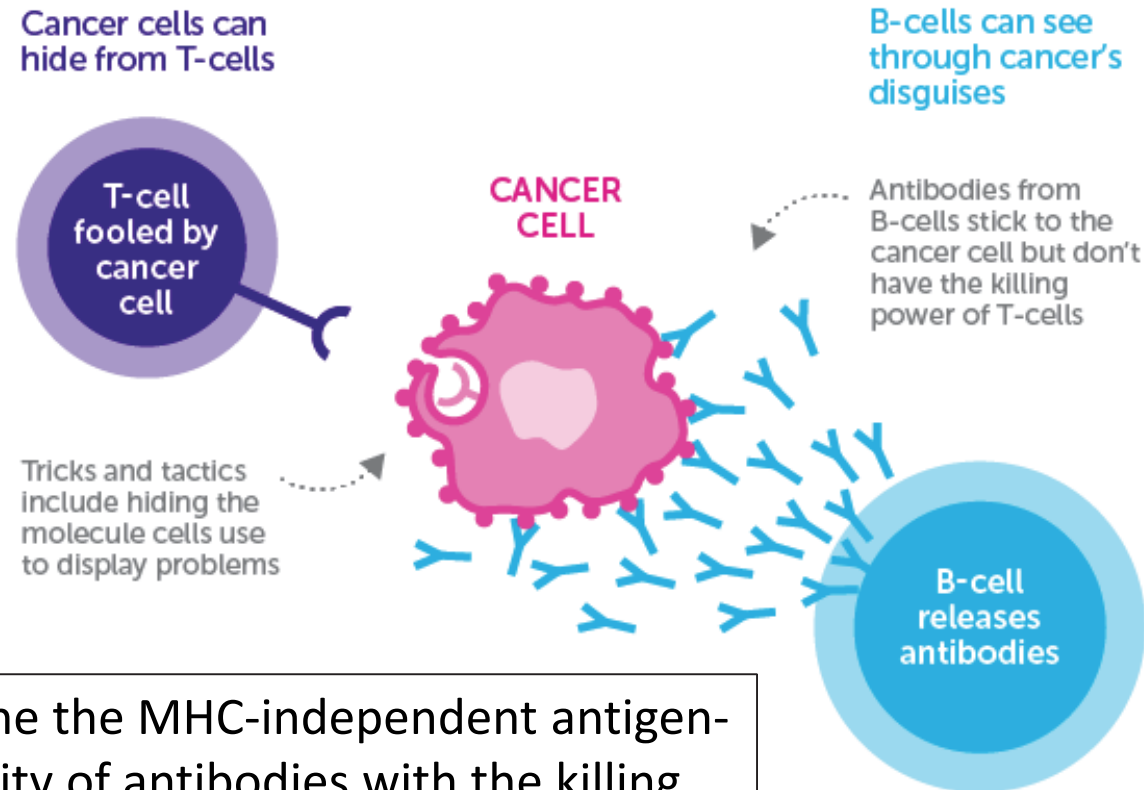
KML-Experten berichten vom EHA 2018 in Stockholm



## 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.

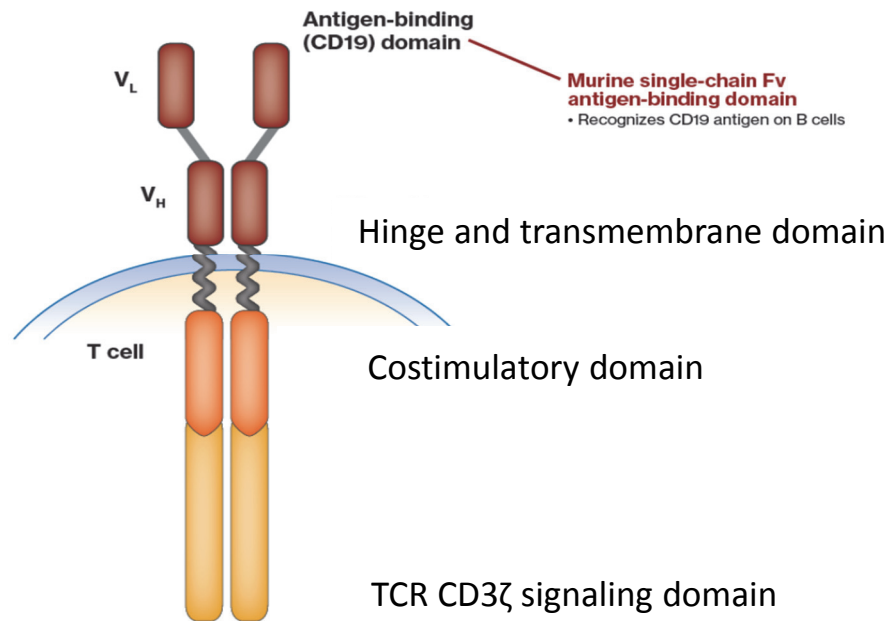
# How can we use the adoptive immune system to fight cancer?



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

Mears, [scienceblog.cancerresearchuk.org](http://scienceblog.cancerresearchuk.org), January 19, 2016

## Chimeric Antigen Receptor (CAR): structure and function

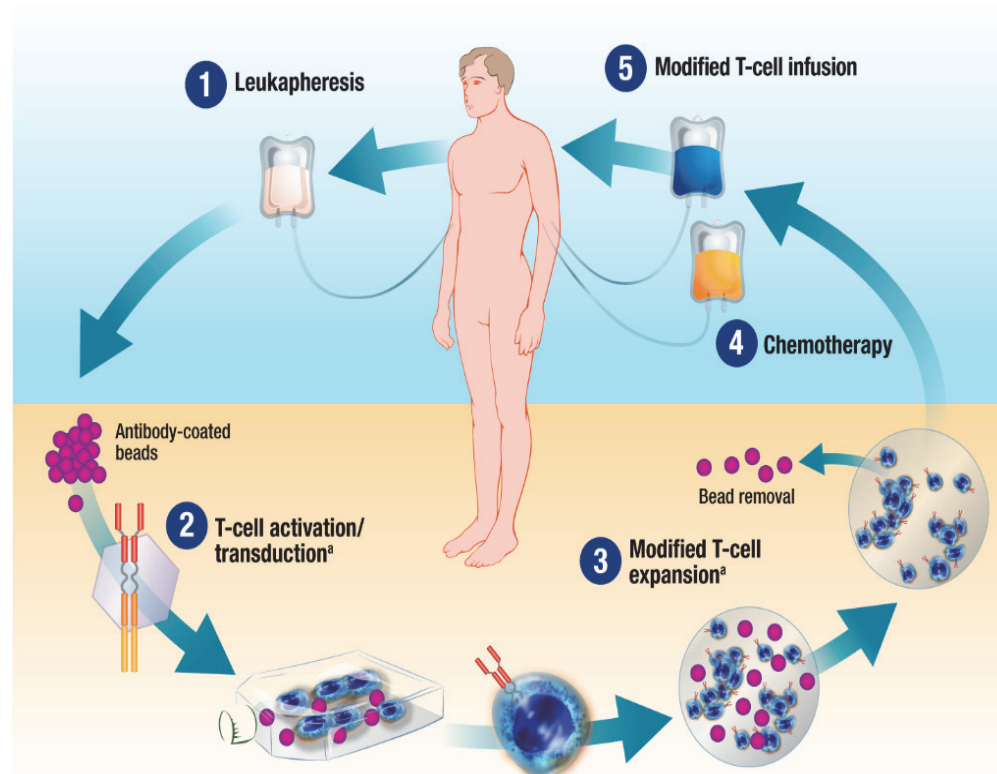


The heavy and light chains of the B cell receptor

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

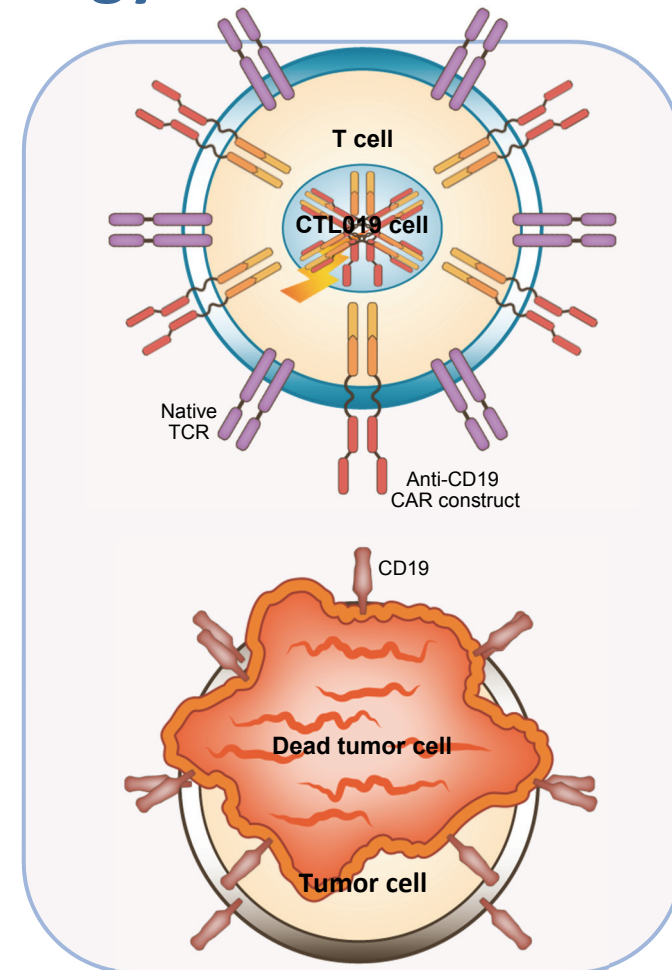
Figure modified based on 1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464. 2. Zhang H, et al. *J Immunol.* 2007;179:4910-4918 and 3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

# Implementation of CAR T-cell technology

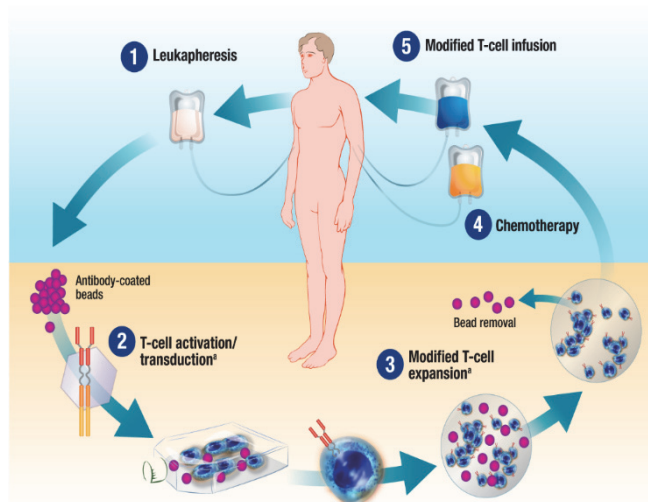


Cellular reprogramming and *ex vivo* expansion are conducted at a cell processing facility.

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.



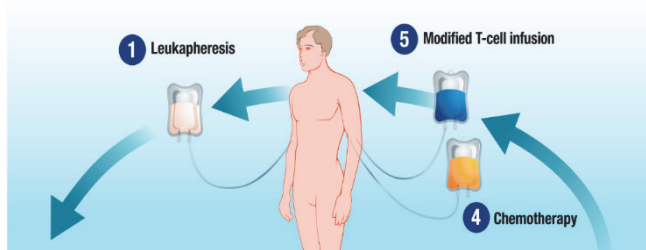
## Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.



vein-to-vein is frozen-to-frozen

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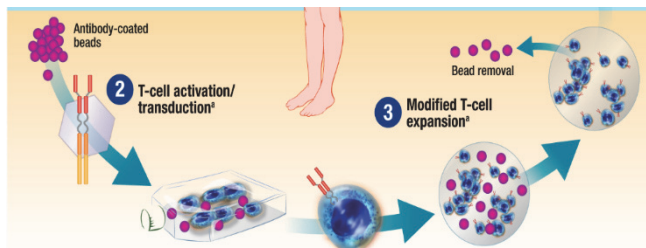
## Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.



Patient in Sweden

Facility in North-  
America

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.

rank,Title,Recruitment,Study Results,Conditions,Interventions,URL

1,CD19-redirected Autologous Cells (CAR-CD19 T Cells),Not yet recruiting,No Results Available,CD19 Positive Malignant B-cell Leukemia and Lymphoma,Genetic: CAR-CD19 T cells Drug: Fludarabine Drug: Cyclophosphamide,https://ClinicalTrials.gov/show/NCT02933775

2,CAR-PA1: Immunotherapy With CD19 CAR T-Cells for CD19+ Haematological Malignancies,Recruiting,No Results Available,Acute Lymphoblastic Leukemia|Burkitt Lymphoma,Procedure: Leukapheresis Drug: Lymphodepletion with fludarabine Drug: Lymphodepletion with cyclophosphamide Biological: CD19 CAR T-cells,https://ClinicalTrials.gov/show/NCT02443831

3,CD19-targeting CAR T Cells for B Cell Lymphoma,Recruiting,No Results Available,B Cell Lymphoma,Biological: CD19-targeting CAR T Cells Infusion,https://ClinicalTrials.gov/show/NCT02547948

4,Immunotherapy With CD19 CAR T Cells for B-Cell Lymphoma,Active,not recruiting,No Results Available,Leukemia|Lymphoma,Biological: Anti-CD19-CAR,https://ClinicalTrials.gov/show/NCT02467739

5,Autologous CD19 CAR T Cells

6,Immunotherapy With CD19 C

7,CD19-targeting 3rd Generat

8,Immunotherapy for high Risk

9,the Sequential Therapy of CD

10,Gene Therapy for B-Cell Non-

11,7A Pediatric and Young Adult

12,Is Clinical Research of Sequen

13,Activated T-Cells Expressing C

14,Phase I Study of CD19-CAR-T2

15,7A Clinical Research of CAR T C

16,CD19-directed CAR T Cells Th

17,7A Pediatric Trial of Genetically

18,7A Study to Assess CD19-targe

19,Memory-enriched CAR-T Cells

20,Anti-CD19 Chimeric Antigen

21,Evaluation of 4th Generation

22,CAR T Cell Receptor Immunot

23,T-cells Expressing Anti-CD19

24,CD19 CAR T Long Term Follow

25,CD19+ CAR T Cells for Lymph

26,Activated T Lymphocytes Exp

27,Competitive Transfer of tACD

28,Adult Diffuse Large Cell Lymph

29,CAR-T Cell Immunotherapy in

30,CAR19 Donor Lymphocytes fr

31,Laboratory Treated T Cells in

32,CD19 Chimeric Receptor Expr

33,Cellular Immunotherapy in T

34,Multivirus CTLs expressing C

35,T Cells Expressing a Fully-hum

36,Memory Enriched T Cells Fol

37,Genetically Modified T-cell in

38,Adult Lymphoblastic

39,Genetically Modified T-cells i

40,Humanized CAR-T Therapy fo

41,CD19 CAR T Cells for B Cell M

42,Cellular Immunotherapy Fol

43,Evaluation of CAR19 T-cells a

44,Anti-CD22 CAR-T Therapy for

45,Administration of Anti-CD19-k

46,Combination Transfer of tACD

47,Study Evaluating the Efficacy

48,High Dose Therapy and Auto

49,Study Evaluating the Efficacy

50,Genetically Modified T-cells i

51,Study Evaluating the Efficacy

52,Treatment of Relapsed and/o

53,CD19-CAR Immunotherapy fo

54,Study Evaluating the Efficacy

55,T-lymphocytes Genetically T

56,JCAR014 and Durvalumab in T

57,CD19 Redirected Autologous

58,Genetically Engineered Lympho

59,Pilot Study of Non-Viral, RNA-Red

60,Genetically Engineered Lympho

## 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**

57,CD19 Redirected Autologous

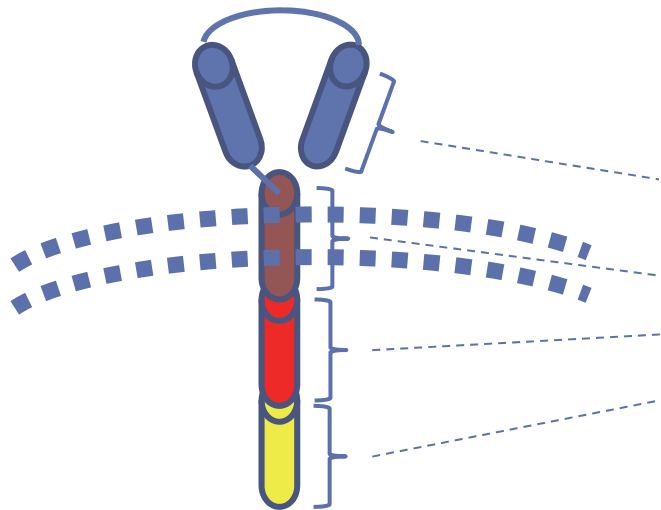
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## CD19 CAR T-Cell Constructs for DLBCL



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 <sup>a</sup>	All Grades, %	Grade 3, %	Grade 4, %
Cytokine release syndrome <sup>b</sup>	58	14	8
Neurological events	21	7	5
Prolonged cytopenia <sup>c</sup>	44	16	16
Infections	34	18	2
Febrile neutropenia	15	13	2

<sup>a</sup> Occurring within 8 weeks of tisagenlecleucel infusion. <sup>b</sup> Cytokine release syndrome was graded using the Penn scale. <sup>c</sup> At day 28.

### No deaths due to tisagenlecleucel, CRS or cerebral edema

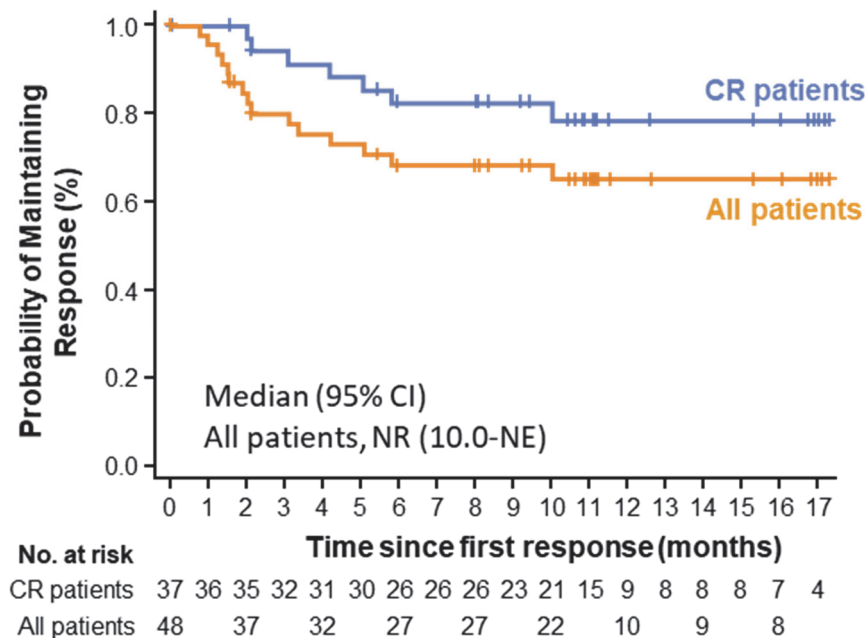
The most common neurological events were

- 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<sup>a</sup>



- 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

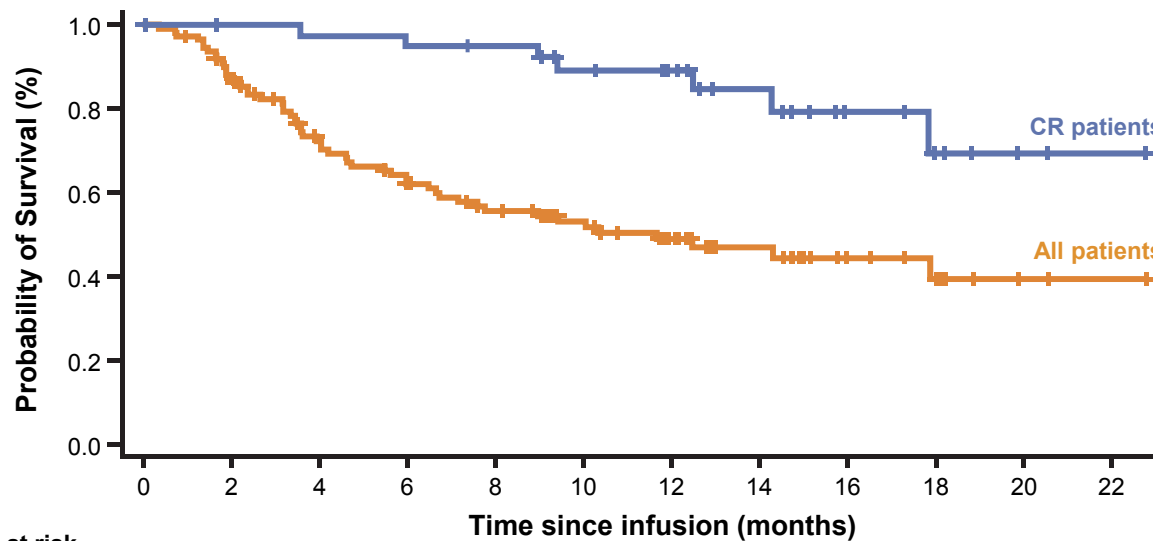
<sup>a</sup> Best ORR within 3 months of infusion.

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

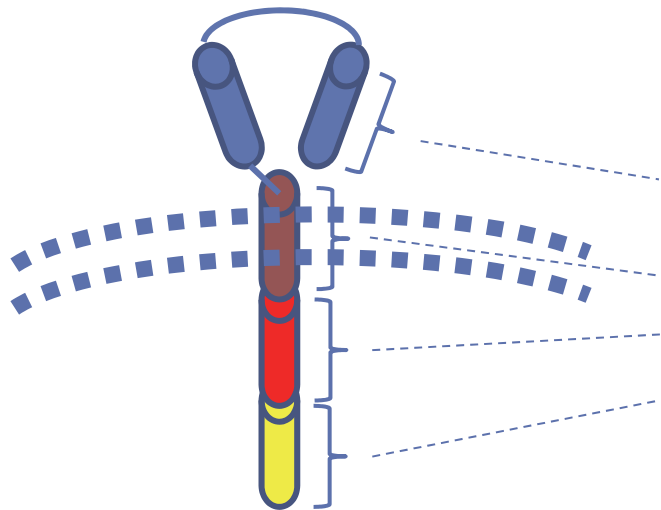
No. at risk	0	2	4	6	8	10	12	14	16	18	20	22										
CR patients	40	40	40	39	39	38	38	37	36	30	29	23	16	16	12	9	9	7	3	2	1	1
All patients	111	94	71	60	50	40	28	19	11	8	2	1										

### Overall survival at 12 mo

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

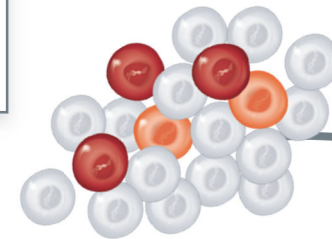
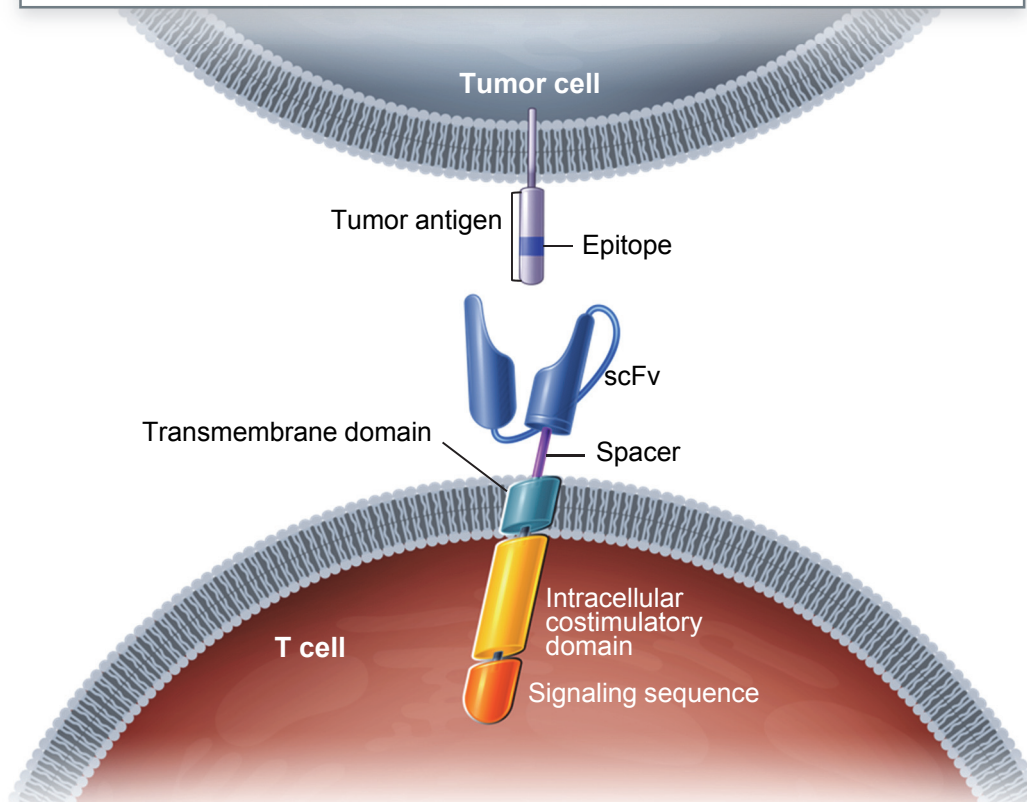
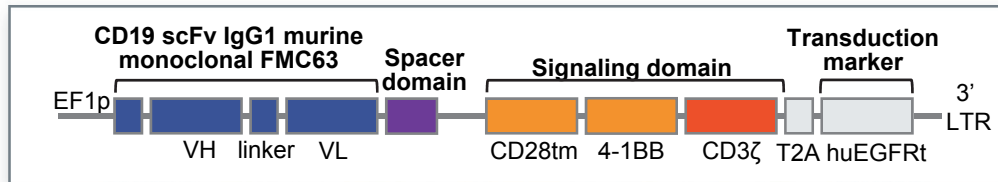
CR, complete response; NE, not evaluable.

## CD19 CAR T-Cell Constructs for DLBCL



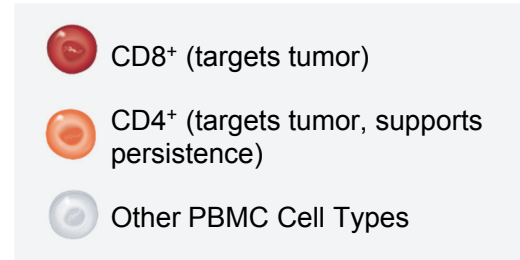
domain	KTE-C19	CTL019	JCAR017
anti-CD19-antibody single chain variable fragment	FMC63	FMC63	FMC63
transmembrane	CD28	CD8	CD28
co-stimulatory	CD28	4-1BB	4-1BB
TCR signaling	CD3ζ	CD3ζ	CD3ζ

# JCAR017: CD19-Targeted Defined Cell Product



Patient's  
PBMCs

- Immunomagnetic selection
- Lentivirus transduction
- Expansion
- Formulated at specified CD4/CD8 composition for Defined Cell Product



CAR<sup>+</sup>CD8<sup>+</sup>

+



CAR<sup>+</sup>CD4<sup>+</sup>



# (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

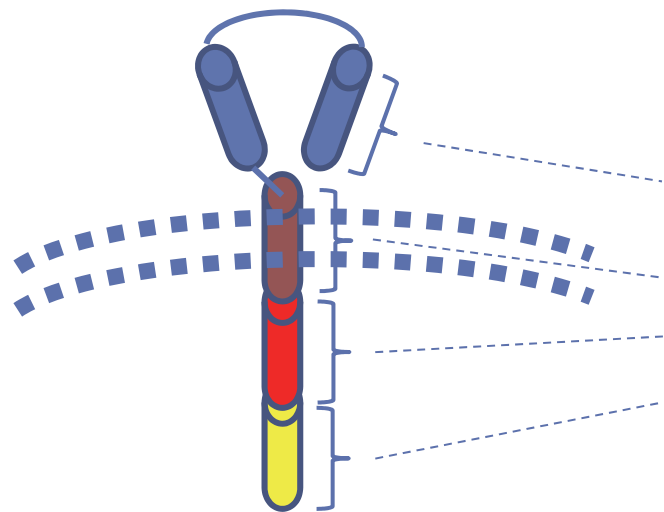
- 91 pts were treated and evaluable for safety
- CRS was seen in 35% of pts; a single pt (1%) developed grade 3-4 CRS.
- Neurotoxicity (NT) developed in 19% of pts including 12% grade 3-4; all but one event resolved at time of data snapshot.
- Nineteen pts (21%) received tocilizumab and/or dexamethasone.

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

### EFFICACY

- Best ORR in FULL (DLBCL, PMCBCL, 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



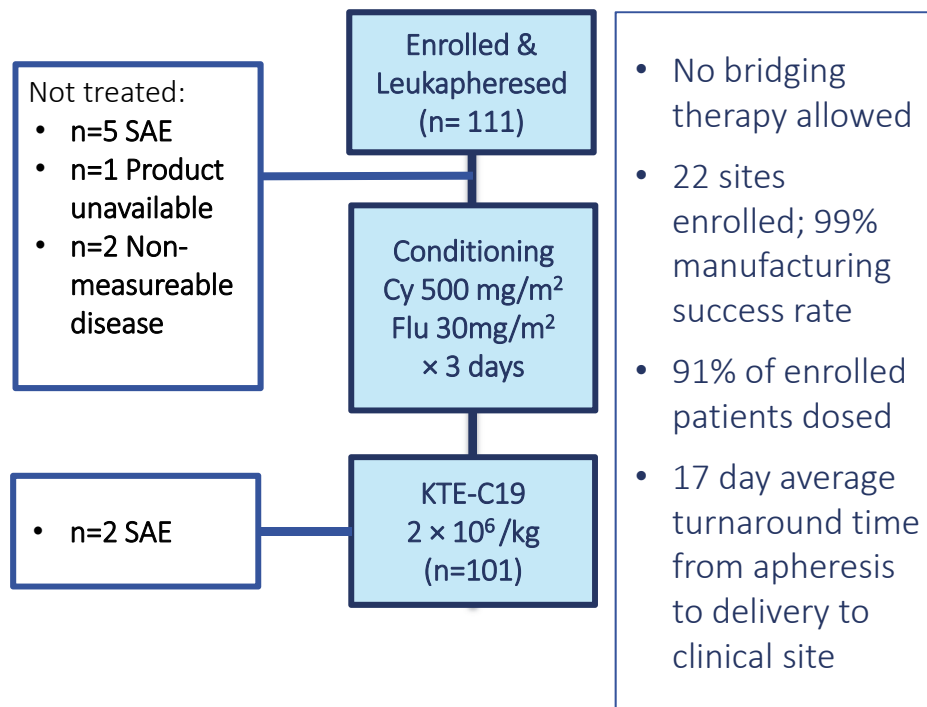
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transmembrane	CD28	CD8	CD28
co-stimulatory	CD28	4-1BB	4-1BB
TCR signaling	CD3ζ	CD3ζ	CD3ζ

# (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 2 <sup>nd</sup> or later-line	56 (77)
Relapse post-ASCT	15 (21)

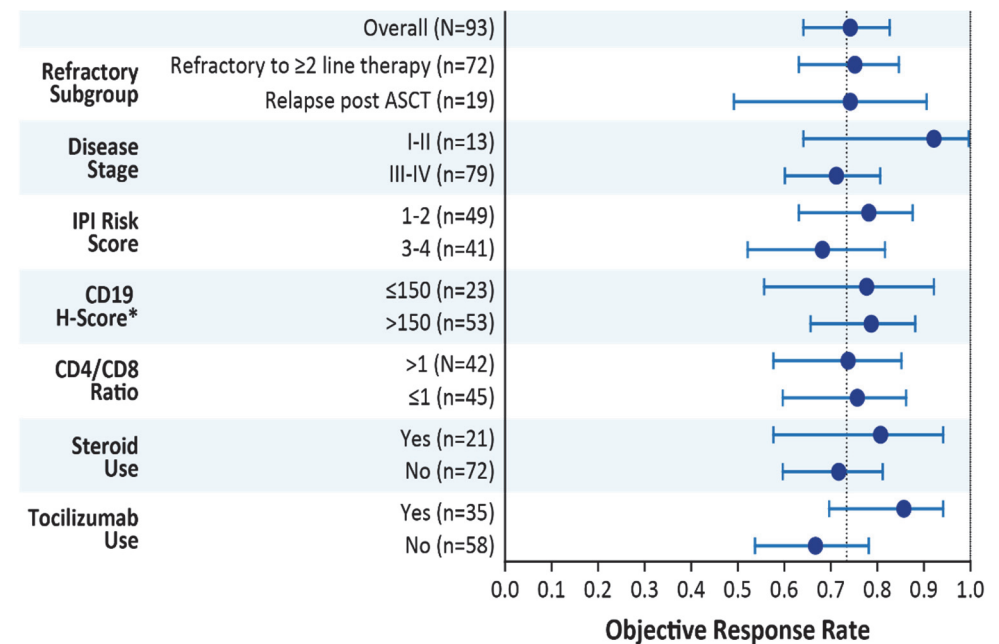
Neelapu et al., N Engl J Med 2017;377:2531-44.

# 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

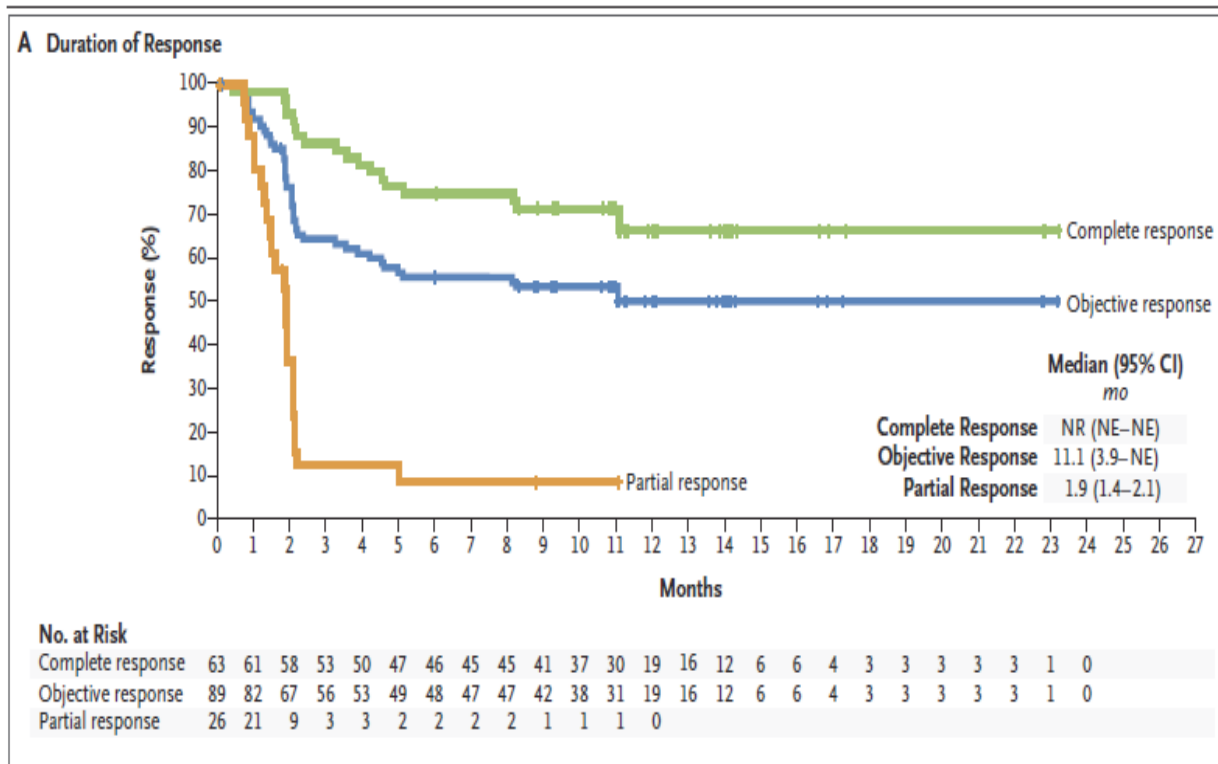


Neelapu et al., N Engl J Med 2017;377:2531-44.

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 Ciloleucele** in the ZUMA-1 Phase II trial: DOR and PFS

Response, % (95% CI)	Lot	
	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 <sup>a</sup>	49 (36 – 61)	51 (35 – 65)
12-month OS <sup>a</sup>	65 (51 – 75)	51 (35 – 65)

<sup>a</sup>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 eine 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!

Die Kurzpräsentationen sind online unter

**[www.lymphome.de/eha2018](http://www.lymphome.de/eha2018)**

Für den Inhalt verantwortlich:

Prof. Dr. med. Peter Borchmann

Klinik I für Innere Medizin • Uniklinik Köln

Das Informationsprojekt wird unterstützt von den Firmen



Diese hatten keinen Einfluss auf die Inhalte.