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Aktuelle Therapiekonzepte mit CAR T-Zellen

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Disclosure of conflict of interests

1. Advisory Role or Expert Testimony:
   Takeda, BMS, Roche, Amgen, Novartis, Celgene, Miltenyi Biotech, Gilead

2. Honoraria:
   Takeda, Novartis, BMS, Roche, MSD, Celgene, Miltenyi Biotech, Gilead, Abbvie

3. Financing of Scientific Research:
   Takeda Oncology, MSD, Novartis

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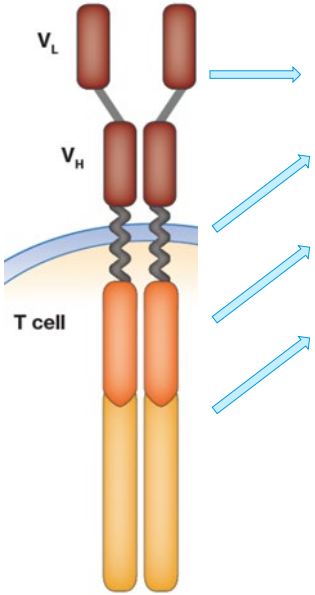
Anti-CD19 CAR T-Cell constructs in LBCL (large B-cell lymphoma)

specificity

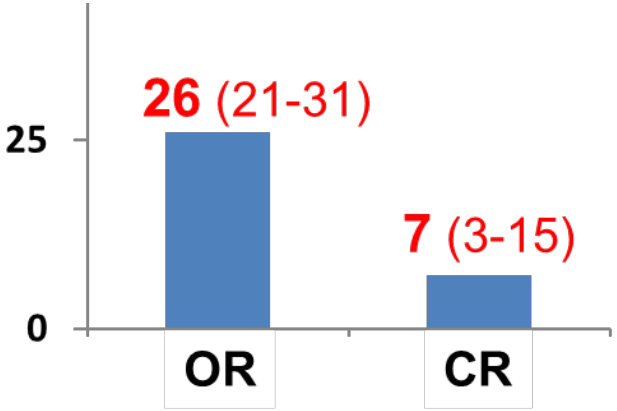


activity

Study drug	KTE-C19	CTL019
Anti CD19 scFv	FMC63	FMC63
transmembrane	CD28	CD8
co-stimulatory	CD28	4-1BB
TCR signaling	CD3ζ	CD3ζ
Generic name	Axicabtagene Ciloleucel	Tisagen-lecleucel
Trade name	**Yescarta**	**Kymriah**
Status	approved	approved

“Chemo” or CAR T-cells for refractory patients? “Best guess evidence” by indirect comparison of **response rates** for SCHOLAR-1 versus CAR T-cell products

Chemotherapy RR DLBCL



Crump et al; Blood 2017

CAR T-cell therapy best ORR DLBCL

	n	ORR	CR
Axicabtagene Ciloleucel	77	82%	38%
Tisagenlecleucel	81	53%	40%

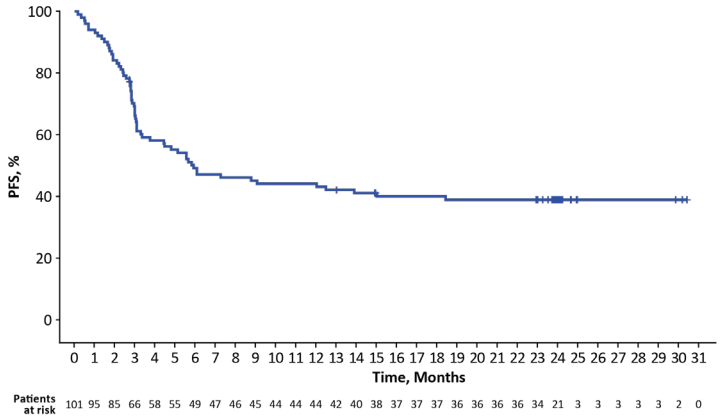
Neelapu et al., N Engl J Med 2017;377:2531-44.

Schuster N Engl J Med 2019

Are these repsones durable? PFS with longer follow-up (pivotal trials).

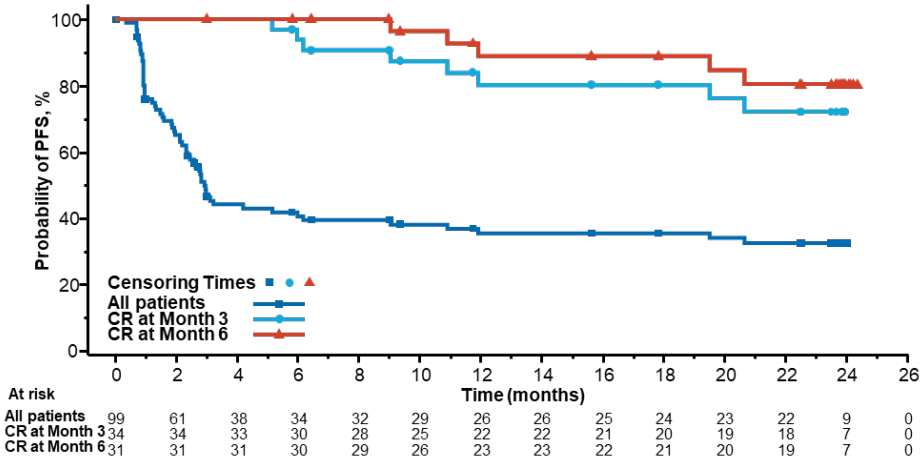
Vergleichbare Remissionsraten mit stabilen PFS Plateaus sind in dieser Situation bisher mit keiner anderen Therapie beschrieben.

Axicabtagene Ciloleucel



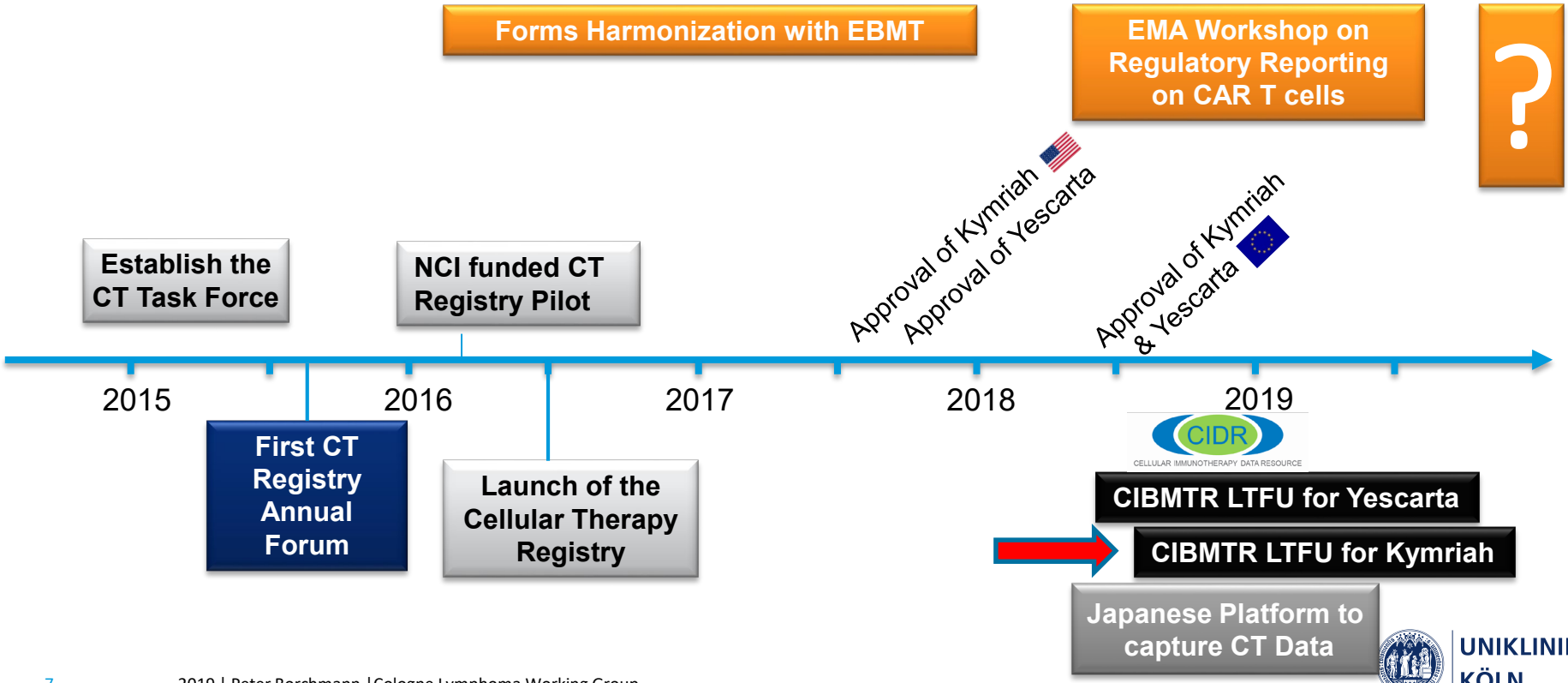
Neelapu et al, ASH 2019

Tisagenlecelucel



Schuster et al., ASH 2019

Real World Experience: Development of the Cellular Therapy Registry



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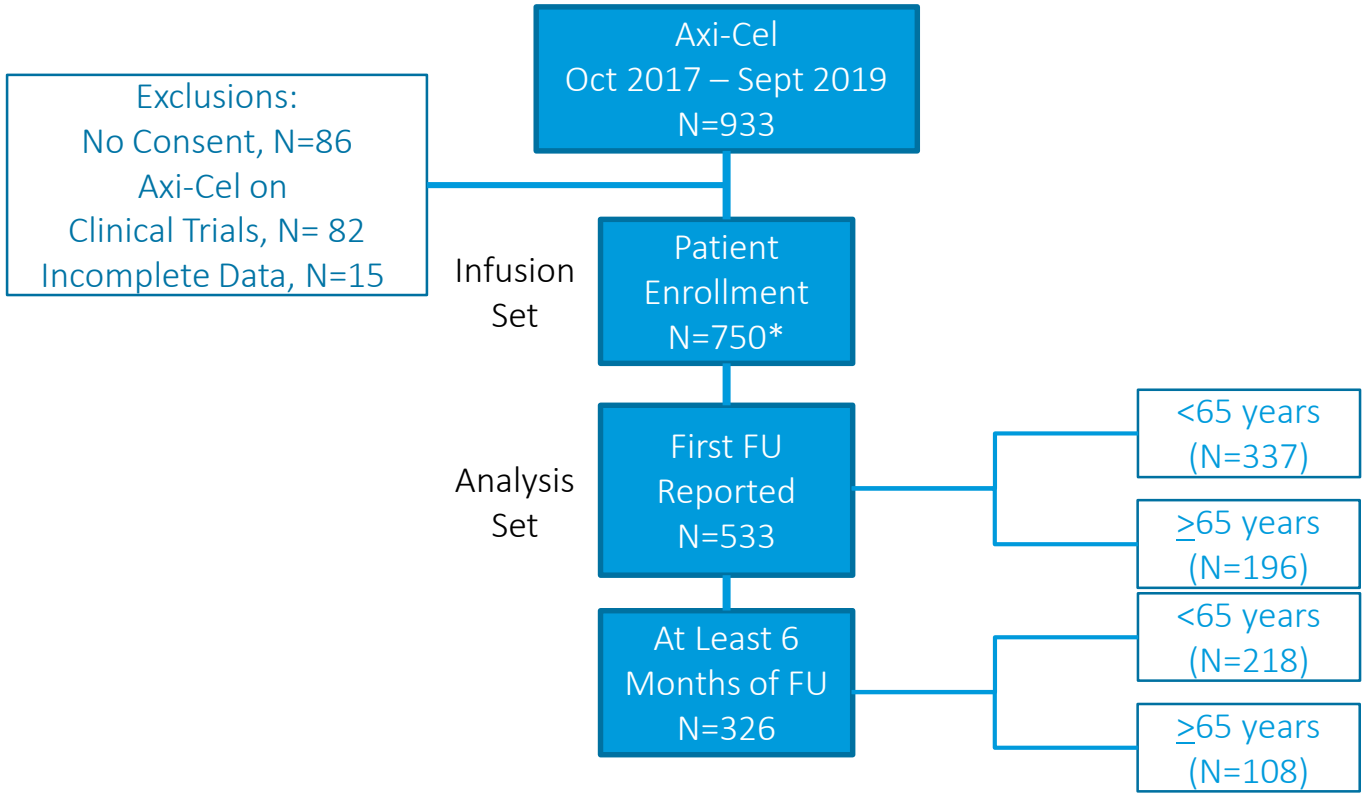
Patient Accrual, Safety and Efficacy Cohorts



Median follow-up 6.2 months (1-16 months)

Pasquini et al., ASH 2019

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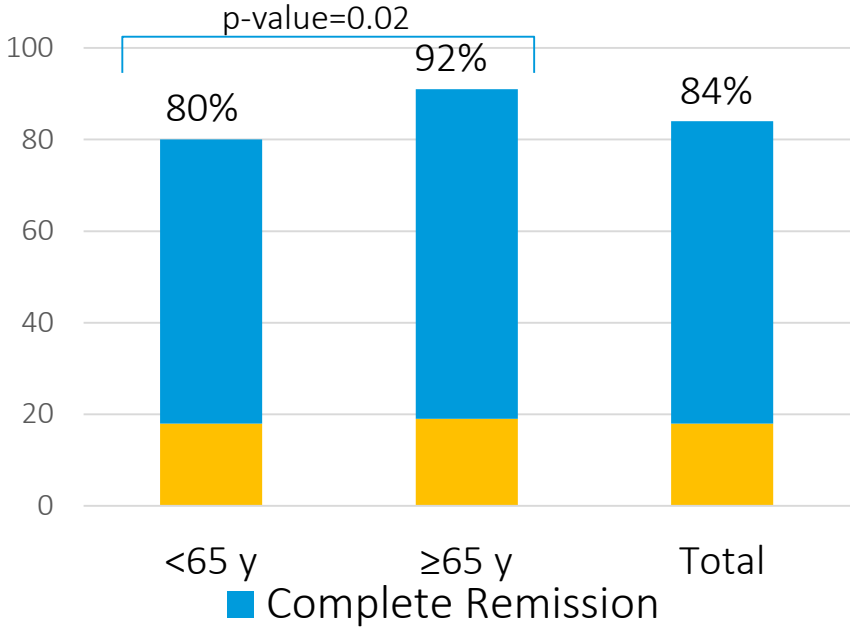
Demographics Compared to ZUMA-1

Characteristic	CIBMTR	ZUMA-1[1]
No. of patients	533	108
Median age, y (range)	**61(19-86)**	**58 (23-76)**
≥ 65 y	37%	25%
Male	66%	68%
ECOG performance status 0-1	80%	100%
>3 prior lines of therapy	66%	70%
Double/triple hit lymphoma	**36%**	**11%**
Prior auto-HCT	**32%**	**25%**
Prior allo-HCT	2%	0
History of CNS lymphoma	1%	0
Prior CAR T-cell	0.9%	0

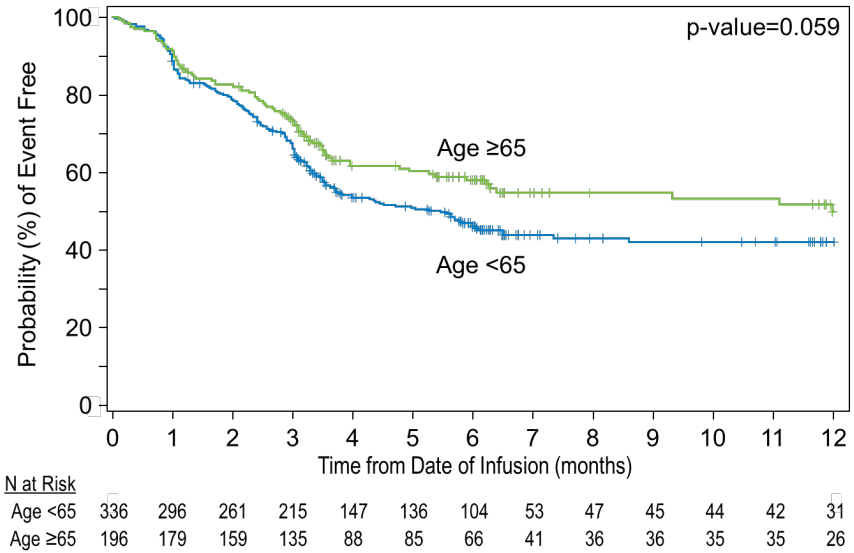
[1]Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544

RWE efficacy: disease response and PFS to Axi-Cel for LBCL

At Least 6 Months Follow-Up, N=326



Progression-Free Survival



Pasquini et al., ASH 2019

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Post-Marketing Use Outcomes of an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, Axicabtagene Ciloleucel

	< 65 y n (%)	> 65 y n (%)	Total n (%)
Pat.	194	101	295
Alter, Median (Spanne)	56 (19-65)	70 (65-81)	61 (19-81)
DLBCL mit HGBL/DH/TH	70 (36)	35 (35)	105 (36)
ECOG 2	10 (5)	5 (5)	15 (5)
Vorherige autologe SZT	64 (33)	35 (35)	99 (34)
CR Rate	90 (46)	63 (62)	153 (52)
CRS Grad ≥ 3	4/14 (9)	8/4 (12)	12/17 (10)
NE all grades	112 (58)	669 (68)	181 (61)
Grade 5 AE	1	1	2
Use of Tozilizumab			70
Use of Steroids			26

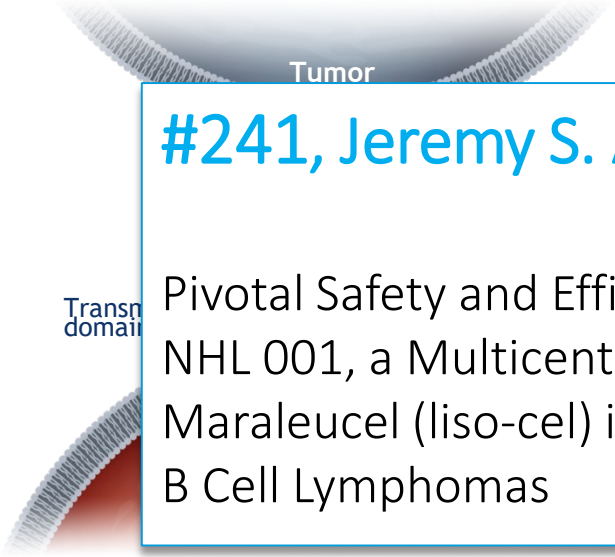
Real World Daten von Axi-Cel und Tisagenlecleucel zusammengefasst:

1. Effektivität der Therapien ist in der Praxis ident zu den Ergebnissen der Zulassungsstudien, obwohl tendenziell ältere Patienten mit mehr Risikofaktoren für Therapieversagen und Nebenwirkungen behandelt wurden.
2. Die Produkte zeigen tendenziell weniger schwere Toxizität als in den Zulassungsstudien, am ehesten wegen des früheren Einsatzes geeigneter Therapeutika.
3. Auch dieses Therapieprinzip ist wirksamer bei weniger Tumorlast: es sollte also besser nicht als „last-line option“ verwendet werden, wenn man den größten Benefit für den Patienten erreichen möchte.

➢ Randomisierte Studien in der Zweitlinie gegen SOC laufen (Zuma-7 (Yescarta), Belinda (Kymriah), Transform Lisocabtagene Maraleucel)

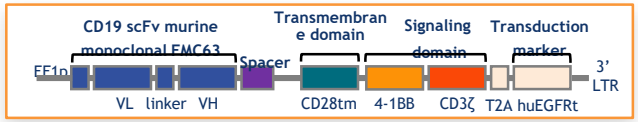
Perspectives: Improving efficacy of CD19 CARs by effector cell composition

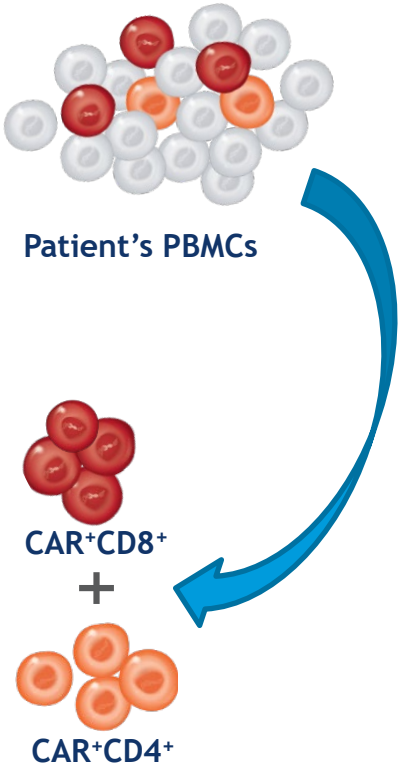
Lisocabtagene Maraleucel (liso-cel; JCAR017), CD19-Directed Defined Cell Product



#241, Jeremy S. Abramson et al.: LISO-CEL

Pivotal Safety and Efficacy Results from TRANSCEND NHL 001, a Multicenter Phase 1 Study of Lisocabtagene Maraleucel (liso-cel) in Relapsed/Refractory (R/R) Large B Cell Lymphomas





CD8⁺ (targets tumor)

CD4⁺ (targets tumor, supports persistence)

Other PBMC cell types

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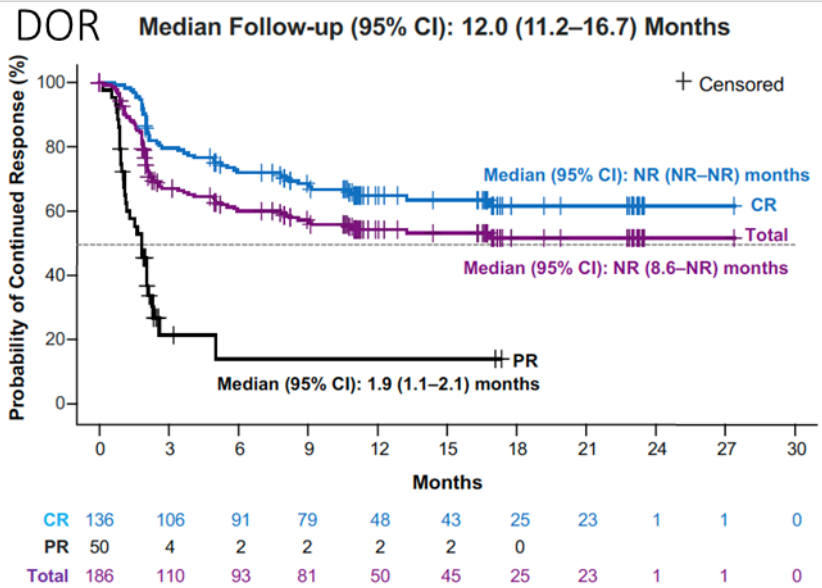
TRANSCEND NHL:

Ein weiteres wirksames Produkt mit ähnlichen Daten, wie wir sie bereits in dieser Indikation von den anderen Produkten kennen.

Efficacy-Evaluable Patients (N=256)	
ORR (95% CI)	73% (67–78)
CR rate (95% CI)	53% (47–59)
Time to first CR or PR, median (range), months	1.0 (0.7–8.9)
DOR at 6 months (95% CI), %	60.4 (52.6–67.3)
DOR at 12 months (95% CI), %	54.7 (46.7–62.0)



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KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Results of the Phase 2 ZUMA-2 Study

Michael Wang,[1] Javier Munoz,[2] Andre Goy,[3] Frederick L. Locke,[4] Caron A. Jacobson,[5] Brian T. Hill,[6] John M. Timmerman,[7] Houston Holmes,[8] Samantha Jaglowski,[9] Ian W. Flinn,[10] Peter A. McSweeney,[11] David B. Miklos,[12] John M. Pagel,[13] Marie José Kersten,[14] Noel Milpied,[15] Henry Fung,[16] Max S. Topp,[17] Roch Houot,[18] Amer Beitinjaneh,[19] Weimin Peng,[20] Lianqing Zheng,[20] John M. Rossi,[20] Rajul K. Jain,[20] Arati V. Rao,[20] and Patrick M. Reagan[21]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Banner MD Anderson Cancer Center, Gilbert, AZ; [3]John Theurer Cancer Center, Hackensack, NJ; Moffitt Cancer Center, Tampa, FL; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Cleveland Clinic Foundation, Cleveland, OH; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA; [8]Texas Oncology, Dallas, TX; [9]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [10]Sarah Cannon Research Institute, Nashville, TN; [11]Colorado Blood Cancer Institute, Denver, CO; [12]Stanford University School of Medicine, Stanford, CA; [13]Swedish Cancer Institute, Seattle, WA; [14]Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [15]CHU Bordeaux, Service D'hematologie et Therapie Cellulaire, F-33000 Bordeaux, France; [16]Fox Chase Cancer Center, Philadelphia, PA; [17]Universitatsklinikum Wurzburg, Wurzburg, Germany; [18]CHU Rennes, Univ Rennes, Inserm & EFS, Rennes, France; [19]University of Miami, Miami, FL, USA; [20]Kite, a Gilead Company, Santa Monica, CA; [21]University of Rochester Medical Center, Rochester, NY

ZUMA-2 Patient Eligibility

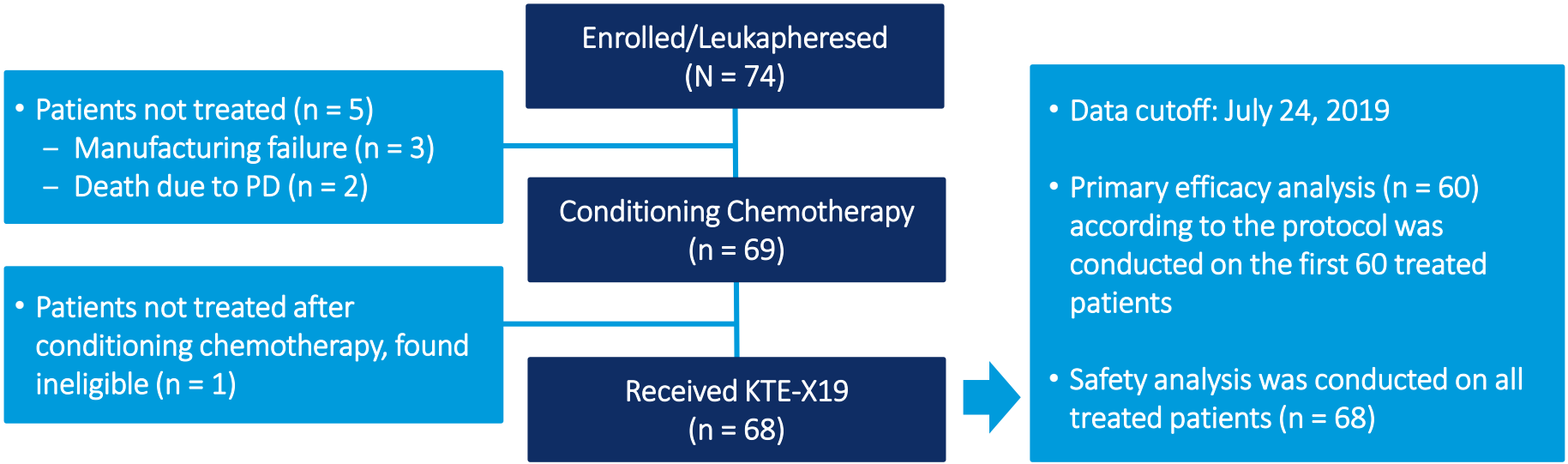
Key Inclusion Criteria

- R/R MCL defined as
  - Disease progression after last regimen or
  - Failure to exhibit a CR or PR to the last regimen
- 1 – 5 Prior therapies that must have included
  - An anthracycline- or bendamustine-containing chemotherapy and
  - Anti-CD20 monoclonal antibody therapy and
  - Ibrutinib or acalabrutinib
- ≥ 1 Measurable lesion
- Age ≥ 18 years
- ECOG of 0 or 1
- Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function
- ALC ≥ 100/µL

Key Exclusion Criteria

- Prior alloSCT
- Prior CD19-targeted therapy
- Prior CAR T cell therapy
- Clinically significant infection
- History of or current CNS involvement by MCL or other CNS disorders

ZUMA-2 Disposition



KTE-X19 was successfully manufactured for 71 patients (96%) and administered to 68 (92%)

Median time from leukapheresis to delivery of KTE-X19 to the study site was 16 days

Cytokine Release Syndrome

No Grade 5 CRS occurred

Parameter	N = 68
CRS, n (%)[a]	
Any grade	62 (91)
Grade ≥ 3	10 (15)
Most common any grade symptoms of CRS, n (%)	
Pyrexia	62 (91)
Hypotension	35 (51)
Hypoxia	23 (34)
AE management, n (%)	
Tocilizumab	40 (59)
Corticosteroids	15 (22)
Median time to onset (range), days	2 (1 – 13)
Median duration of events, days	11
Patients with resolved events, n (%)	62/62 (100)

Neurologic Events

Parameter	N = 68
Neurologic events, n (%)[a]	
Any grade	43 (63)
Grade ≥ 3	21 (31)
Most common any grade symptoms, n (%)	
Tremor	24 (35)
Encephalopathy	21 (31)
Confusional state	14 (21)
AE management, n (%)	
Tocilizumab	18 (26)
Corticosteroids	26 (38)
Median time to onset (range), days	7 (1 – 32)
Median duration of events, days	12
Patients with resolved events, n (%)	37/43 (86)[b]

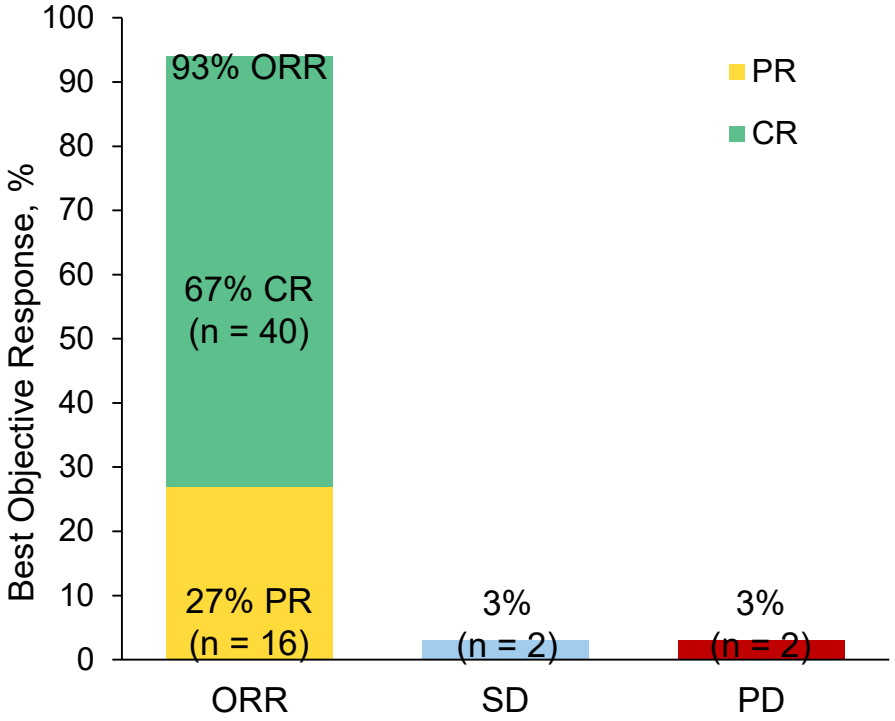
[b] Four patients had ongoing neurologic events at data cutoff: Grade 1 tremor (n = 3), Grade 2 concentration impairment (n = 1), and Grade 1 dysesthesia (n = 1).

No Grade 5 neurologic events occurred

One patient had Grade 4 cerebral edema confirmed by MRI of the brain

- The patient was intubated and treated with aggressive multimodality therapies including tociluzumab, siltuximab, high-dose steroids, intrathecal Ara C plus dexamethasone, mannitol, ventriculostomy and IV ATG[c]
- The neurotoxicities fully resolved and the patient remains in CR 30 months later
- This is the first reported use of ATG in treating CAR T cell-related toxicities

ORR by IRRC Assessment Was 93% (95% CI, 84 – 98) and CR Rate Was 67% (95% CI, 53 – 78)



	Efficacy-Evaluable N = 60
Median follow-up (range), mo	12.3 (7.0 – 32.3)
Patients with ≥ 24 mo follow-up, n (%)	28 (47)
Median time to response (range), mo	
Initial response	1.0 (0.8 – 3.1)
CR	3.0 (0.9 – 9.3)
Patients converted from PR/SD to CR, n (%)	24 (40)
PR to CR	21 (35)
SD to CR	3 (5)

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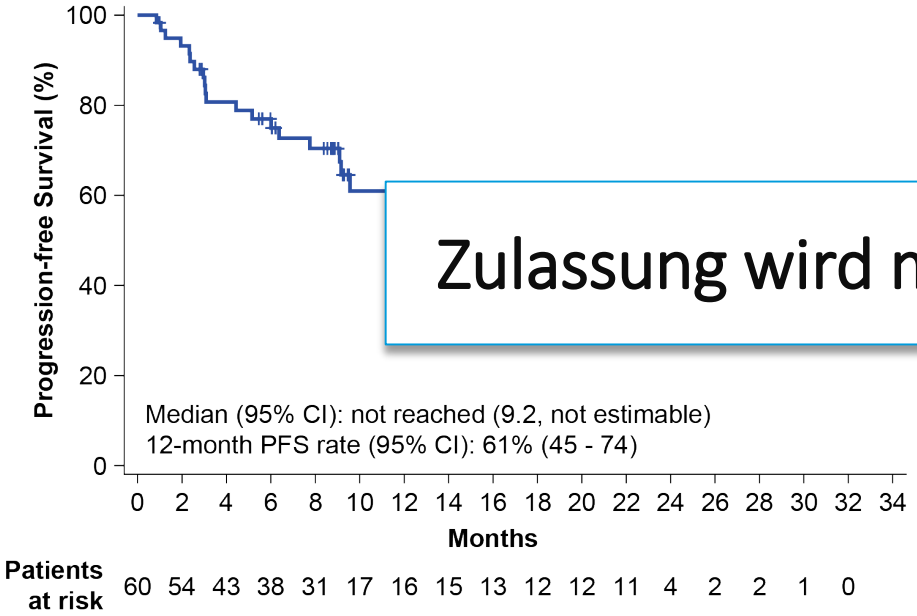
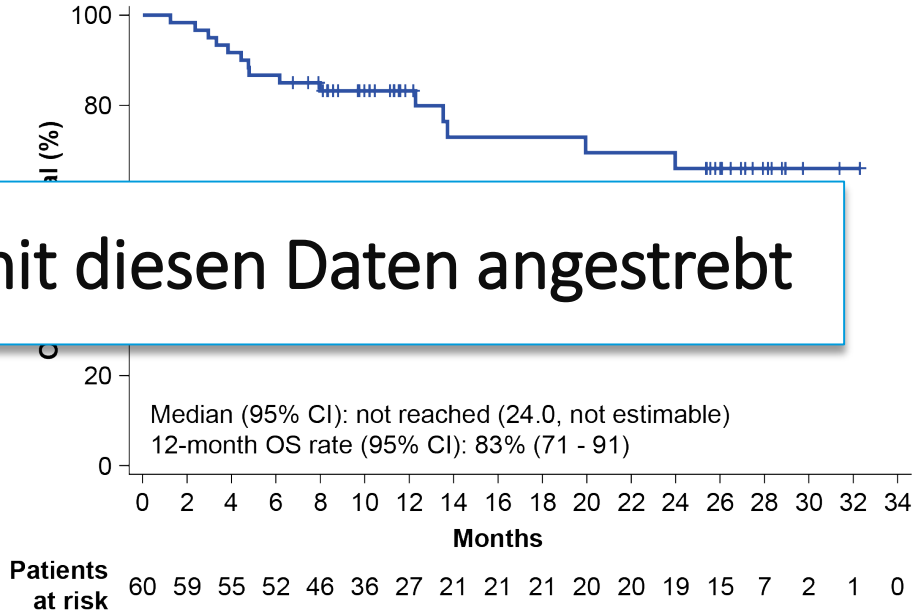
Progression-Free Survival and Overall Survival

Median PFS and median OS were not reached after a median follow-up of 12.3 months





Zulassung wird mit diesen Daten angestrebt

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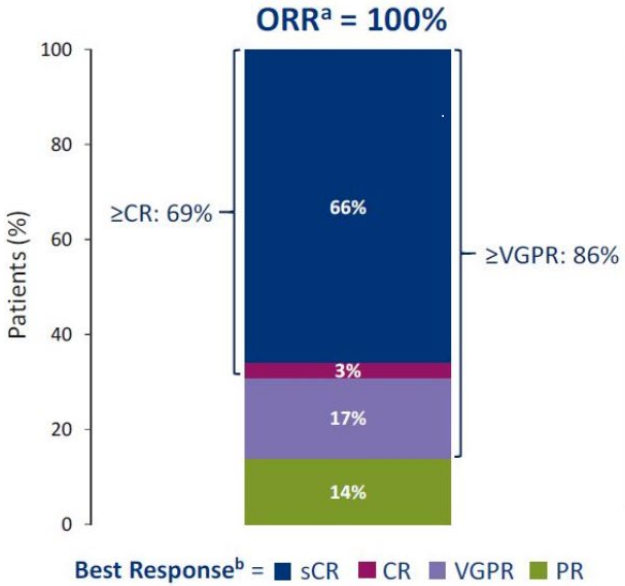
577: Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen (BCMA), in Patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM)

Deepu Madduri *et al.*, New York, USA.

- **n=29 mit JNJ-4528-Infusion**
- **Alter 61 Jahre**, **5 vorausgegangene** Behandlungszyklen, **88% triple-refraktar** gegen PI +IMiD + CD38-Antikorper, Dosis: 0.73x106 CAR+ cells/kg
- CRS (88%), Neutropenie (80%), Anämie (76%), Thrombozytopenie (72%)
- CRS (im Mittel) 7d nach Infusion, Dauer 4d, Gabe von Tocilizumab (91%) oder Corticosteroiden (27%), begleitend Neurotoxizitat bei n=3 (nach 1-2 d limitierend)

577: Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528

CARTITUDE-1: Early, Deep Responses and High Response Rate

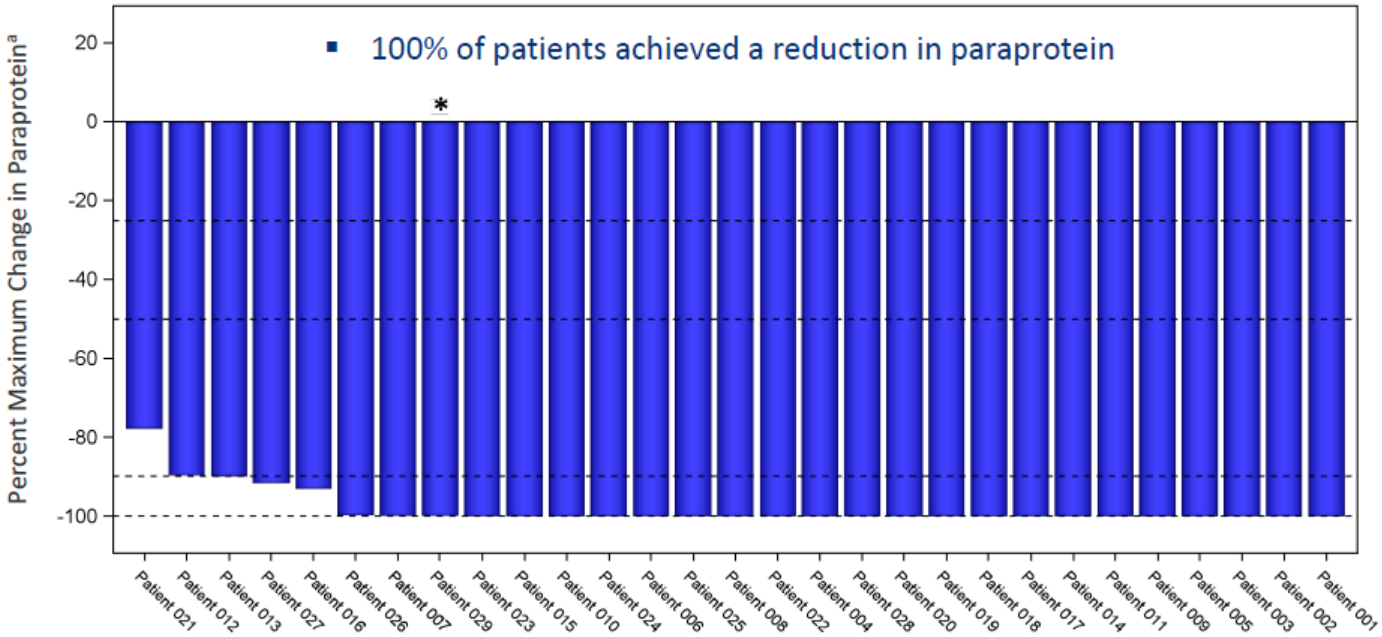


- N=29, median follow-up = 6 months (range, 3 – 14)
- Median time to first response = 1 mo (1 – 3)
- Median time to ≥ CR = 1 mo (1 – 9)
- 100% of patients evaluable for MRD were MRD-negative
- 27 / 29 patients remain progression free at 6 months median follow-up

[a]PR or better; Independent Review Committee-assessed, [b]No patient had stable disease or progressive disease as best response. CR=complete response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

ASH Press Briefing CAR-T and Beyond, 61st ASH Annual Meeting 2019, Madduri D et al. on Abstract #577

577: Results from CARTITUDE-1 (JNJ-4528): Tumor Borden Reduction



[a]Serum M-protein, urine M-protein, or difference between involved and uninvolved free light chain (dFLC).*Bence-Jones proteinuria at baseline, with a transient response during bridging therapy; output represents dFLC value

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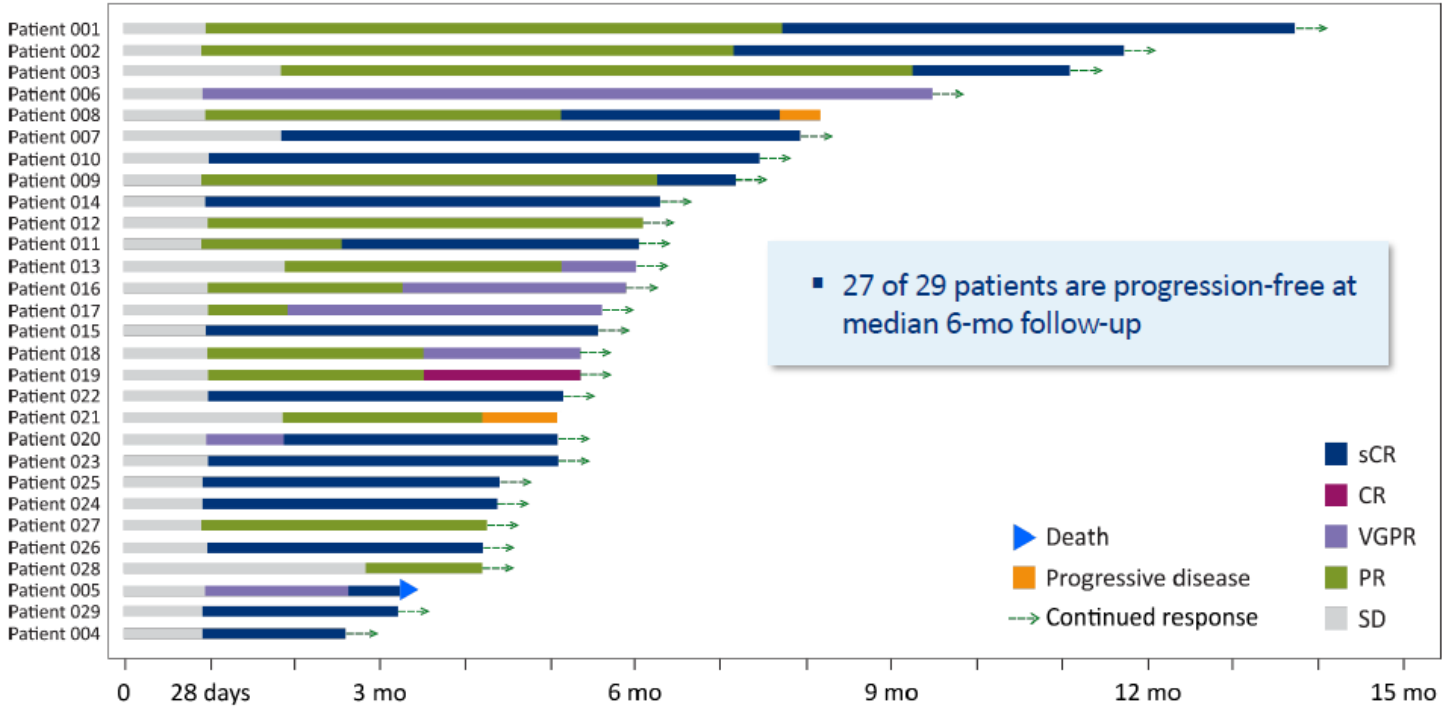
577: Results from CARTITUDE-1 (JNJ-4528): Duration of Response



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577: Results from CARTITUDE-1 (JNJ-4528): Zusammenfassung

- Frühes Ansprechen auf JNJ-4528 bei einer Zieldosis von 0.75x106 CAR+ cells/kg mit hoher Rate an MRD Negativität bei allen evaluierbaren Patienten und vertretbarem Sicherheitsprofil
- Übereinstimmung von CARTITUDE-1- und LEGEND-2-Studie
- 0.75x106 CAR+ cells/kg als empfohlene Phase-II-Dosis (RP2D) bestätigt zur klinischen Weiterentwicklung

➢ Auch wenn die Beobachtungsdauer und die frühe Phase der Studie zur Vorsicht mahnen, so scheint dieses Konstrukt doch sehr wirksam zu sein. Es gibt Unterschiede im Nebenwirkungsprofil im Vergleich zu den CD19 Konstrukten.

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CAR T-Zelltherapie 2019/20: Status quo

- Die „RWE“ bestätigt die Phase II Zulassungsstudien von Tisa-Cel und Axi-Cel hinsichtlich Wirksamkeit und Verträglichkeit trotz ungünstigerer Patientencharakteristika in der Regelversorgung
- Gute Daten für CD19 re-directed CARs vom ASH 2019 auch
  - beim MCL (Axi-Cel ZUMA-2) und
  - bei der CLL (Lisa-Cel, Transcend-004)
- Beim MM ist mit der CARTITUDE Studie eine Studie mit sehr tiefem Ansprechen und vielversprechender Dauer des Ansprechens auf dem ASH 2019 gezeigt worden

➢ **Insgesamt beginnt diese neue Therapieform aufgrund guter Wirksamkeit breiter in den Alltag vorzudringen, zunächst bei verschiedenen konventionell-refraktären hämatologischen Neoplasien**

CAR Team Cologne

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Mareike Tamm
Teresa Vahle
Christina Misch

Project Management
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Vielen Dank für Ihre Aufmerksamkeit!
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Matthias Kochanek

DCLLSG
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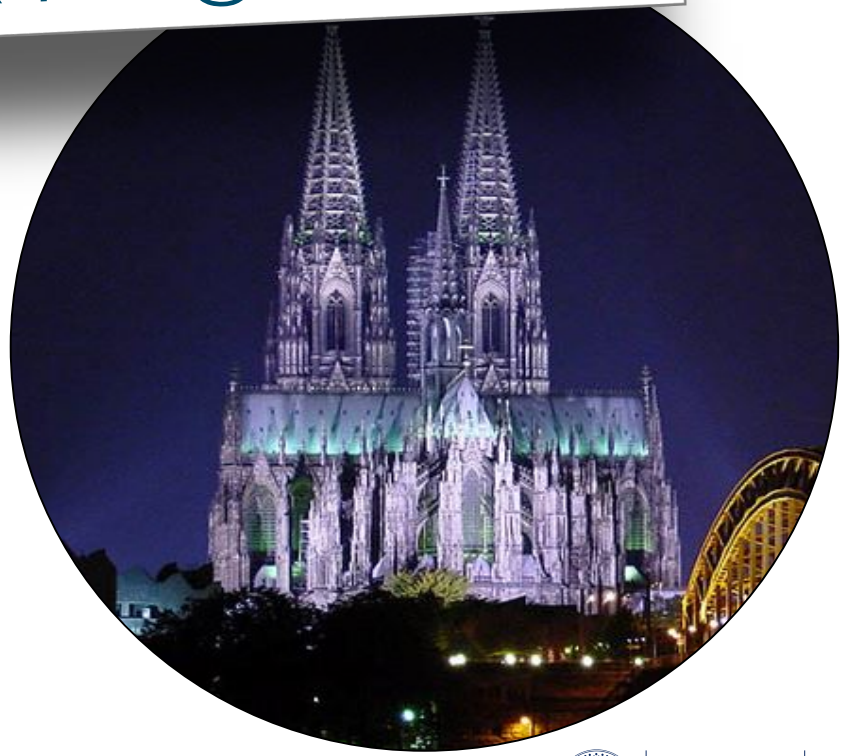

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