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# CAR-T ZELLEN: REPROGRAMMIERUNG DES IMMUNSYSTEMS


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LINDE TILLEULS ACADEMY

# DLBCL: Prognose

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**Rezidiv/Progression innerhalb 1 Jahr → schlecht**

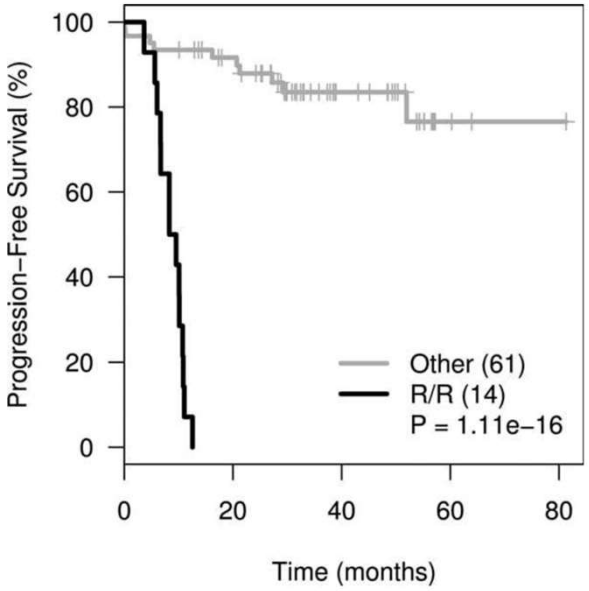
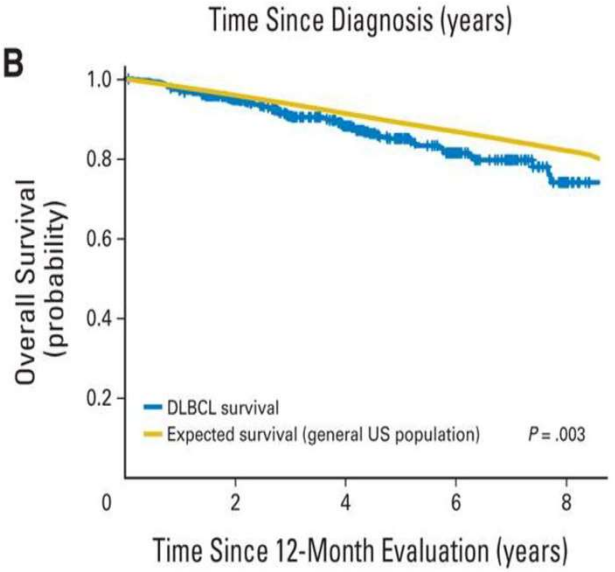



Figure 1. Progression-Free Survival of the R/R cohort. Kaplan-Meier curves comparing the 14 R/R patients selected for sequencing (relapse or progression under treatment in less than a year) to the rest of the available cohort.

Mareschal et al., Genes, Chromosomes & Cancer 2016

**EFS > 12 Monate → exzellent**




Maurer M J et al. JCO 2014;32:1066-1073

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# DLBCL: Behandlung

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Relapse/progression within 1 year → poor

EFS > 12 months → excellent

1. *Hit early and hard* ("one shot disease")
2. Neue Konzepte ausserhalb Chemotherapie
3. Wiederherstellung der immunologischen Kontrolle

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# Warum kann das Immunsystem Infektionen aber nicht Krebs erkennen und bekämpfen?

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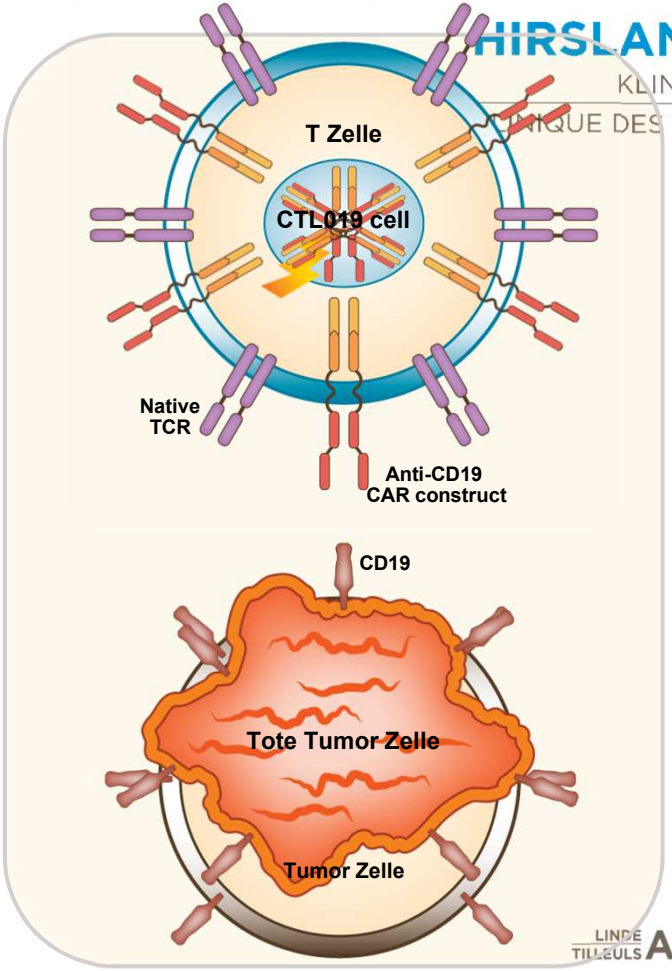
# Umprogrammierung eigener Abwehrzellen

**Kann das eigene Immunsystem so verändert werden, dass es den Tumor erkennt und zerstört?**





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.

# Umprogrammierung eigener Abwehrzellen
## *> 20 Jahre Entwicklungsarbeit*

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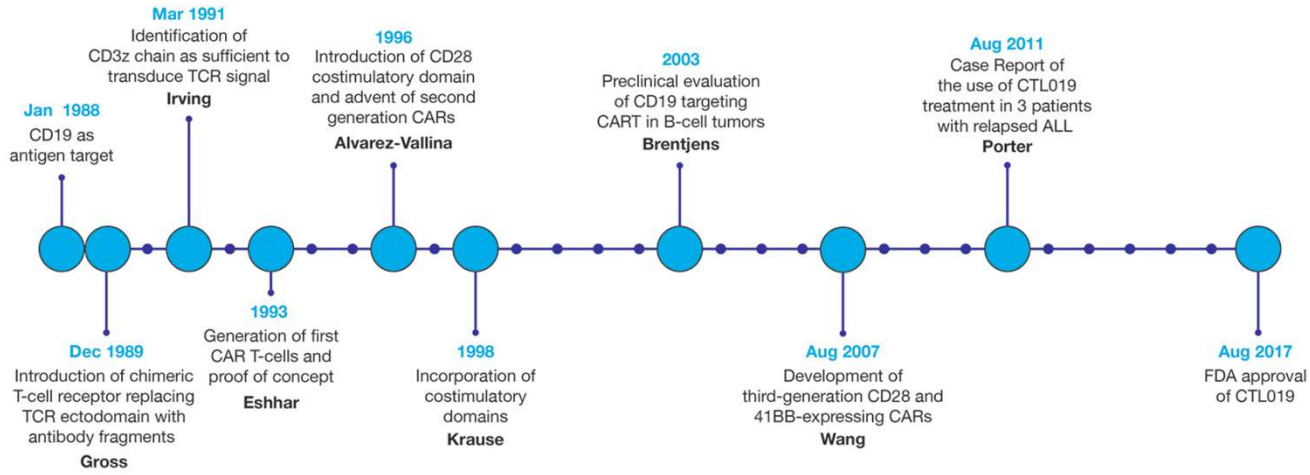


Filley AC et al., Front. Oncol. 8:453 (2018)

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# Emily Whitehead

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- Mit 5 Jahren akute Lymphatische Leukämie (B-ALL) diagnostiziert
- Nach mehreren Rückfällen 2011 zur CAR-T-Zelltherapie zugelassen
- Heilung trotz geringer Erprobung der Therapie
- Eine der ersten Patienten/innen
- Rückfallfrei seit CAR T Therapie
- Berühmt: Treffen mit Obama
- Emily Whitehead Foundation

# Der CAR T-Zellprozess (2)

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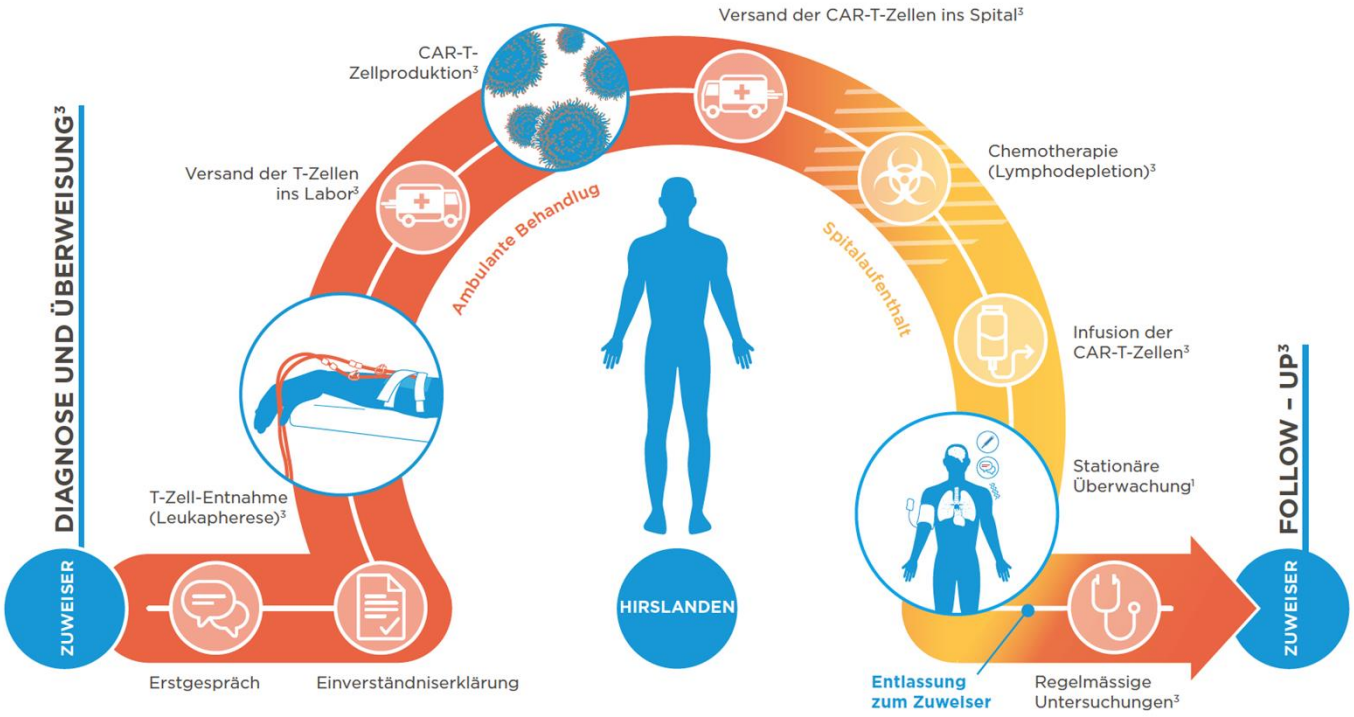


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# CAR T-Zellen bei DLBCL Patienten

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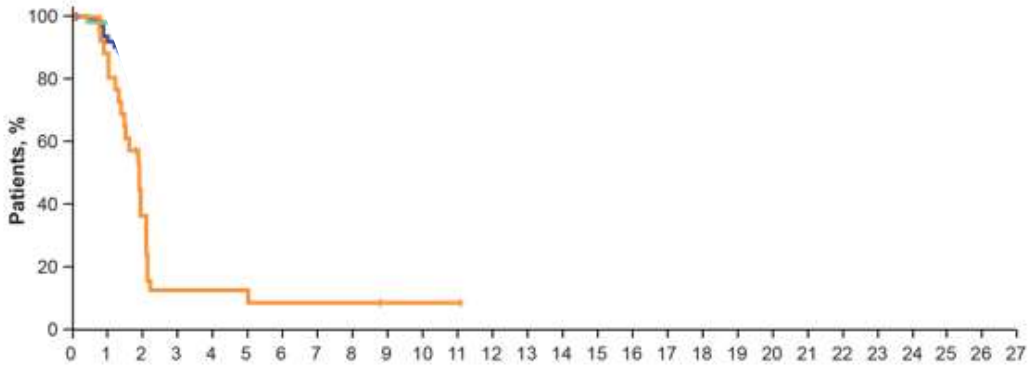
## ZUMA-1: Duration of Response by Best Objective Response




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

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

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

Locke et al., Lancet Oncol. 2019

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# CAR T-Zellen bei DLBCL Patienten

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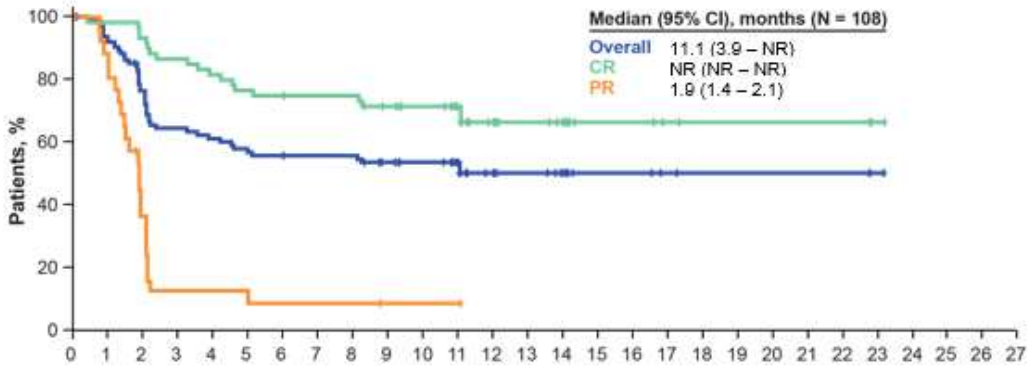


| Patients at Risk | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 89 | 82 | 67 | 56 | 53 | 49 | 48 | 47 | 47 | 42 | 38 | 31 | 19 | 16 | 12 | 6 | 6 | 4 | 3 | 3 | 3 | 3 | 3 | 1 | 0 |
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| PR | 26 | 21 | 9 | 3 | 3 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 0 | | | | | | | | | | | | |

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Locke et al., Lancet Oncol. 2019

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# rrDLBCL: CAR T-Zellen Therapien im Vergleich

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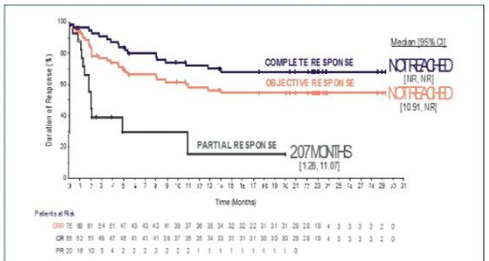
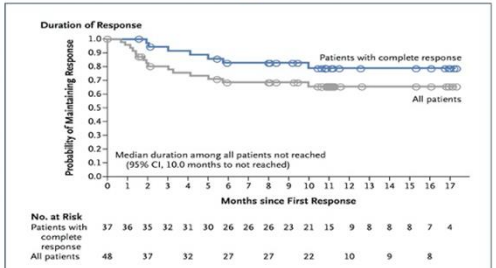
## CD19CAR T Cell Therapy Has changed the outlook of R/R DLBCL

### ZUMA-1: Axi-cel


Median follow-up 27.1 mo
- ORR 83%
- CR 58%
- Ongoing CR 35%
- 2 year OS: 50.5%; EFS: 40%

### JULIET: Tisagenlecleucel




Median follow-up 15 mo
- ORR 54%
- CR 40%
- Ongoing CR 37%
- 1 year OS: 49%


Locke et al. Lancet Oncology 2019; Shuster et al. NEJM 2019

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# Aggressive Lymphome

## - Reihenfolge der Rezidivtherapie -

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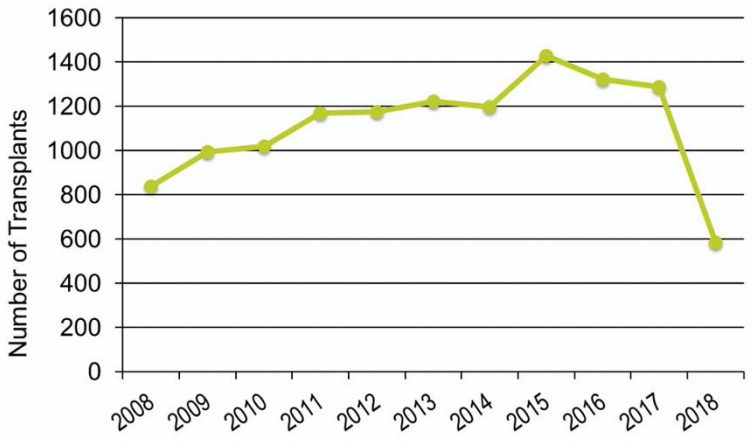
1. Hochdosistherapie mit autologer Transplantation
2. CAR T-Zell Therapie

### DLBCL Trends for Auto-HCT in the US




Warum weniger Fälle?

Shah NN et al., #8000, ASCO 2020

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# Aggressive Lymphome

## - Hochdosischemotherapie + ASCT im Rezidiv -

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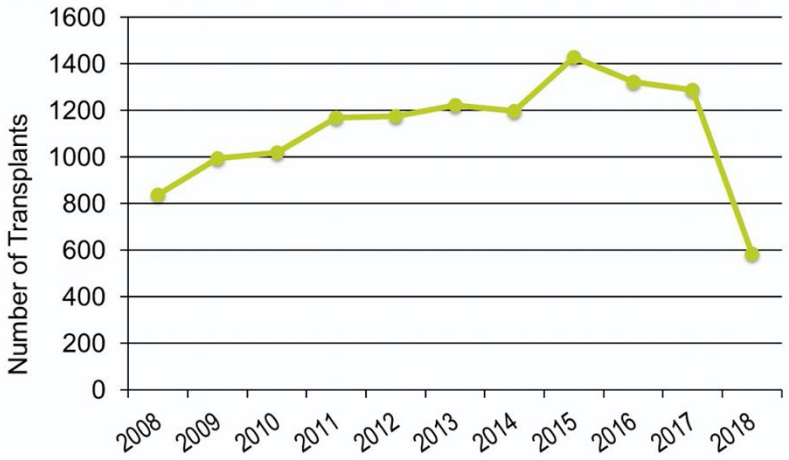
### DLBCL Trends for Auto-HCT in the US




45% decrease in autologous transplant volume in 2018 from prior years suggesting that some patients with chemosensitive disease and a partial response are proceeding with other treatments, presumably CAR T-cell therapy

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# Rezidivtherapie aggressiver Lymphome

## - Transplantation oder CAR T-Zell Therapie? -

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**Kite Announces Yescarta® CAR T-cell Therapy Improved Event-Free Survival by 60% Over Chemotherapy Plus Stem Cell Transplant in Second-Line Relapsed or Refractory Large B-cell Lymphoma**

***-- Landmark ZUMA-7 Study was Initiated in 2017 as the First Randomized Clinical Trial to Test the Earlier Use of a CAR T-cell Therapy Against Standard of Care --***

***-- Study Met the Primary and Key Secondary Endpoints of Event-Free Survival and Objective Response Rate, Demonstrating a Highly Statistically and Clinically Significant Improvement Compared to Standard of Care --***

Press release GILEAD, June 28, 2021 08:30 AM EDT

LINDE TILLEULS ACADEMY

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…. with a median follow-up of two years, the study met the primary endpoint of event-free survival (EFS; hazard ratio 0.398, p <0.0001). The study also met the key secondary endpoint of objective response rate (ORR). The interim analysis of overall survival (OS) showed a trend favoring Yescarta….

Press release, June 28, 2021 08:30 AM EDT

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# CAR T: Relevante Nebenwirkungen

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1. Es kommt zu einer übermässigen Aktivierung des Immunsystems.

2. Damit entstehen primär grippe-ähnliche Beschwerden

   - Cytokine-release Syndroms (CRS)
   - Neurotoxizität (NT)
   - Hämophagozytose-Syndrom (HLH)

# CRS und Neurotoxizität

## - Zeitlicher Verlauf -

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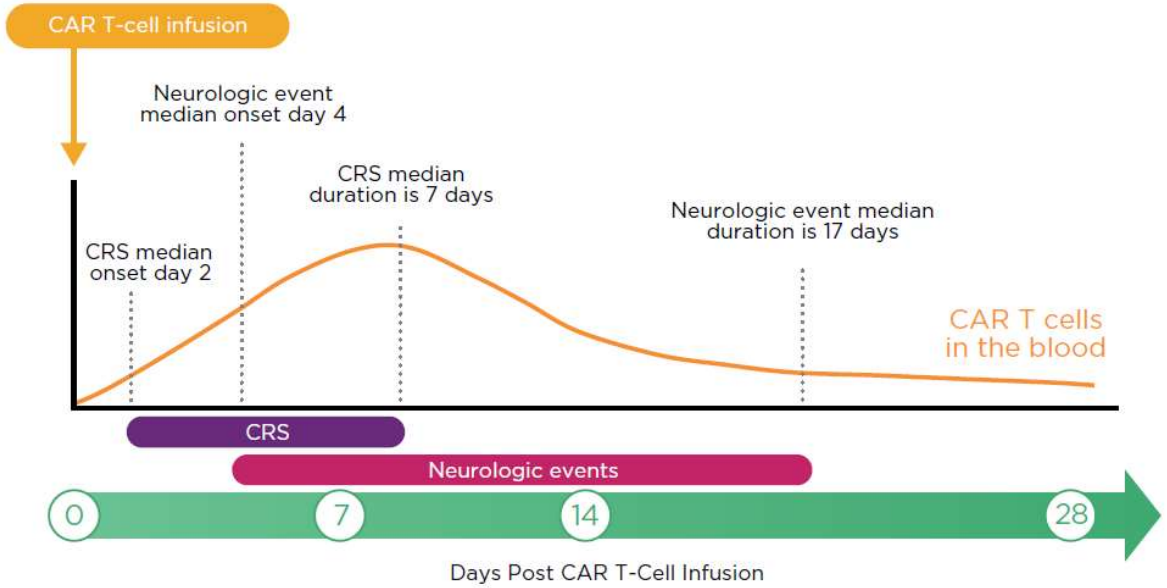


Adkins et al. J Adv Pract Oncol 2019

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# CRS und Neurotoxizität

- Zytokinprofil und therapeutischer Ansatz -

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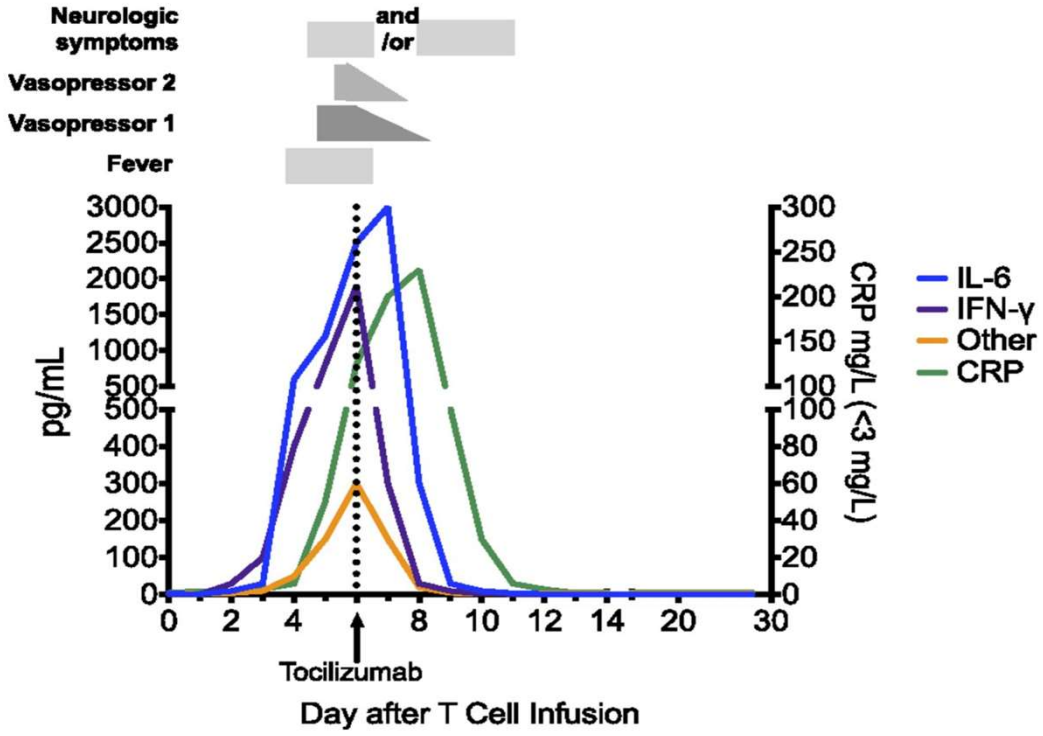


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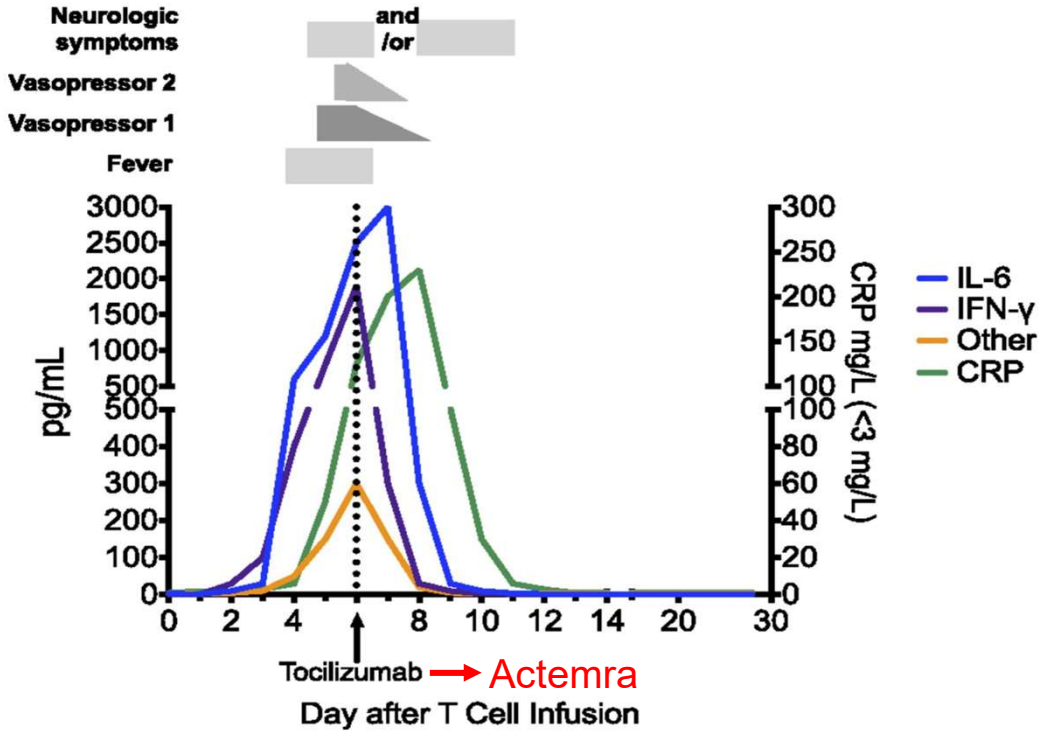


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# Warum betreiben wir den Aufwand?

- Fallzahlen Schweiz (pro Jahr) -

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| Entität | CAR T Zell Fallzahlen CH/J | CAR T Zell Fallzahlen HIRS/J | Zulassung |
|---|---|---|---|
| Akute Leukämie | 15-20 | 0 | 1/2020 |
| Lymphom (DLBCL) | 80-100 | 5-10 | 1/2020 |
| Multiples Myelom | 200-300 | 30 | 9/2021 ? |
| Solide Tumoren | ??? | ??? | ??? |

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# CAR T-Zell Therapie bei Myelompatienten

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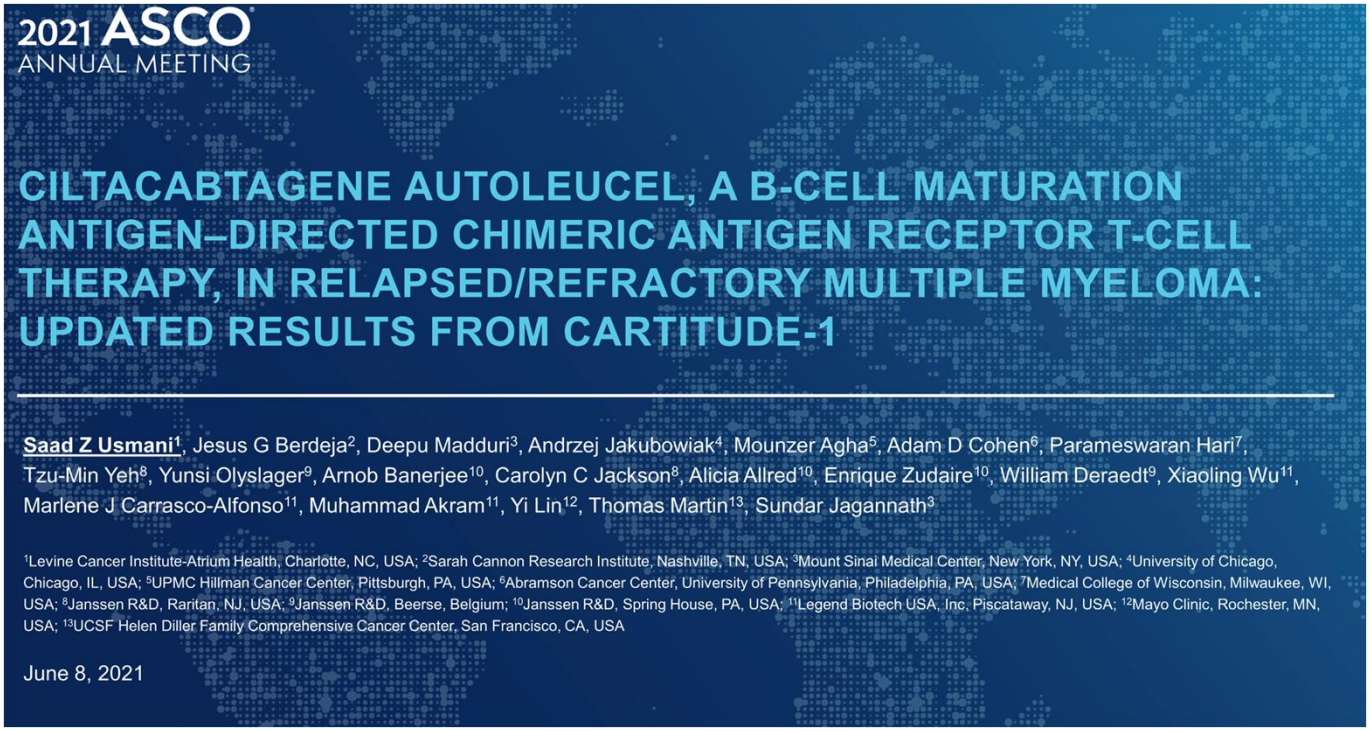


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# CAR T-Zell Therapie bei Myelompatienten

## - Wirksamkeit auch im fortgeschrittenen Stadium -

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| Characteristic | |
|---|---|
| Prior lines of therapy, median (range) | 6.0 (3–18) |
| Prior lines of therapy, n (%) | |
| 3 | 17 (17.5) |
| 4 | 16 (16.5) |
| ≥5 | 64 (66.0) |
| Previous stem-cell transplantation, n (%) | |
| Autologous | 87 (89.7) |
| Allogeneic | 8 (8.2) |
| Triple-class exposed,[c] n (%) | 97 (100) |
| Penta-drug exposed,[d] n (%) | 81 (83.5) |
| Triple-class refractory[c] | 85 (87.6) |
| Penta-drug refractory[d] | 41 (42.3) |
| Refractory status, n (%) | |
| Carfilzomib | 63 (64.9) |
| Pomalidomide | 81 (83.5) |
| Anti-CD38 antibody | 96 (99.0) |
| Refractory to last line of therapy, n (%) | 96 (99.0) |

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# CAR T-Zell Therapie bei Myelompatienten

## - Wirksamkeit auch im fortgeschrittenen Stadium -

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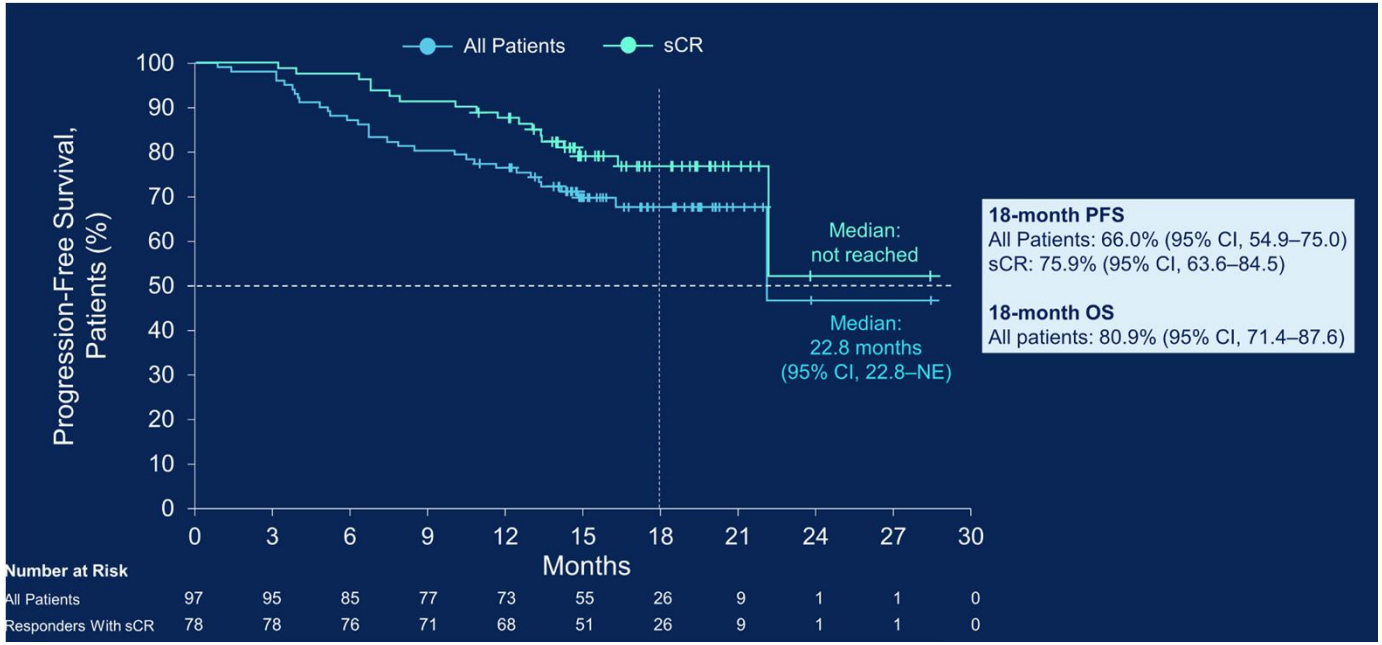


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# PLEURAMESOTHELIOM FAP+ – PHASE I STUDIE:
## ADOPTIVER TRANSFER IN MENSCHEN (U. PETRAUSCH)

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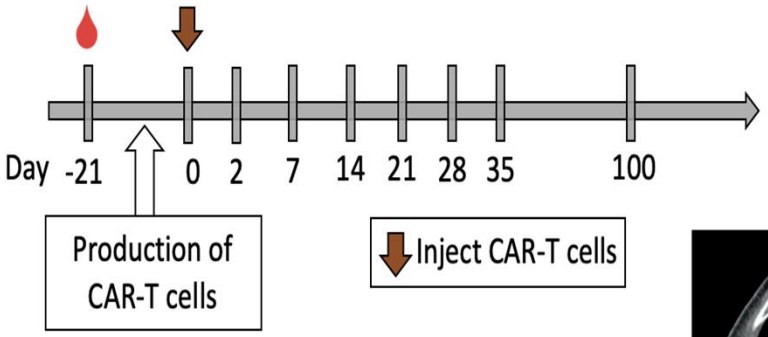
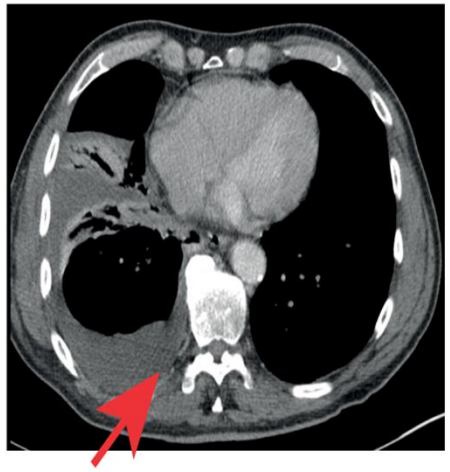
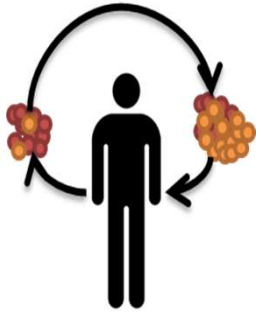



**Patient's profile**

- MPM patient – histologically confirmed FAP
- Age – 74 years, male
- First diagnosed in Nov 2014
- 1 million Δ-CD28 CAR-T cells in pleural effusion





Hiltbrunner et al. Annals of oncology 2021



Gulati et al., Clin Can Res 2018

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# Dynamische Entwicklung bei soliden Tumoren?

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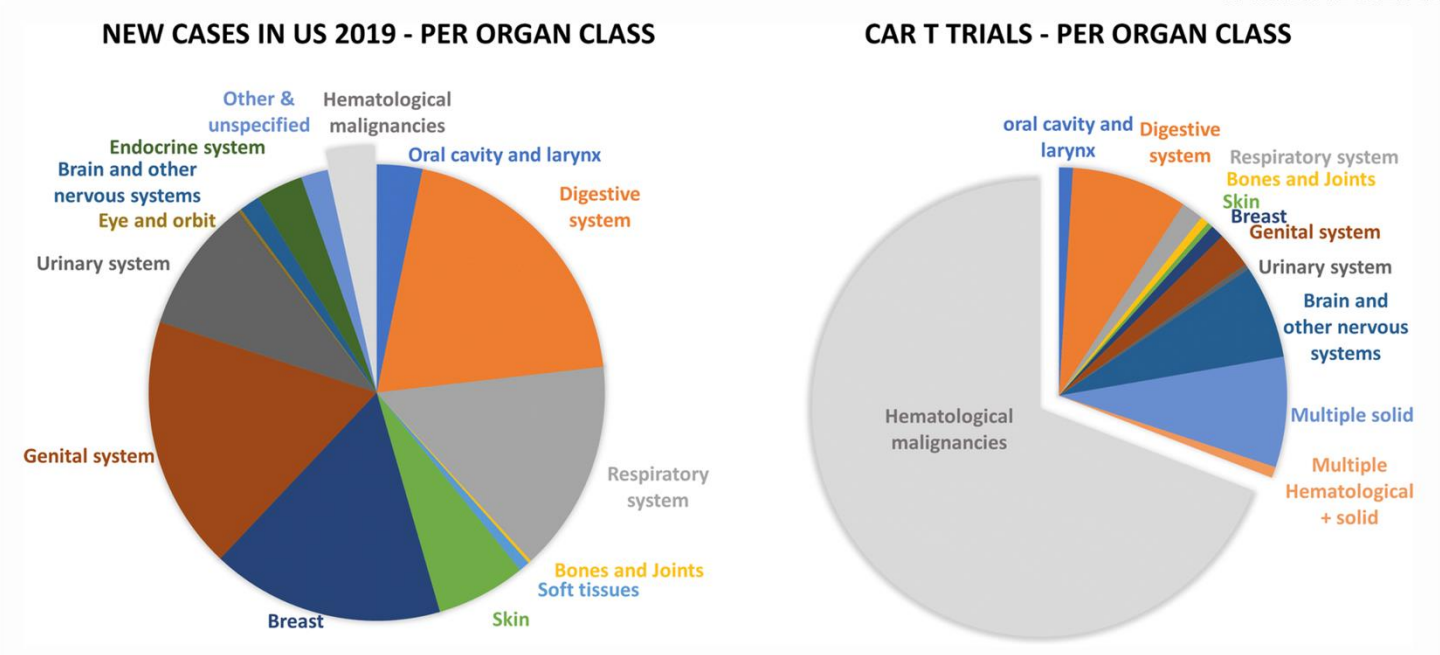


Springuel, L., Lonez, C., Alexandre, B. *et al.* Chimeric Antigen Receptor-T Cells for Targeting Solid Tumors: Current Challenges and Existing Strategies. *BioDrugs* **33,** 515–537 (2019). https://doi.org/10.1007/s40259-019-00368-z

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# CAVE: Effektivität bei soliden Tumoren (noch) geringer



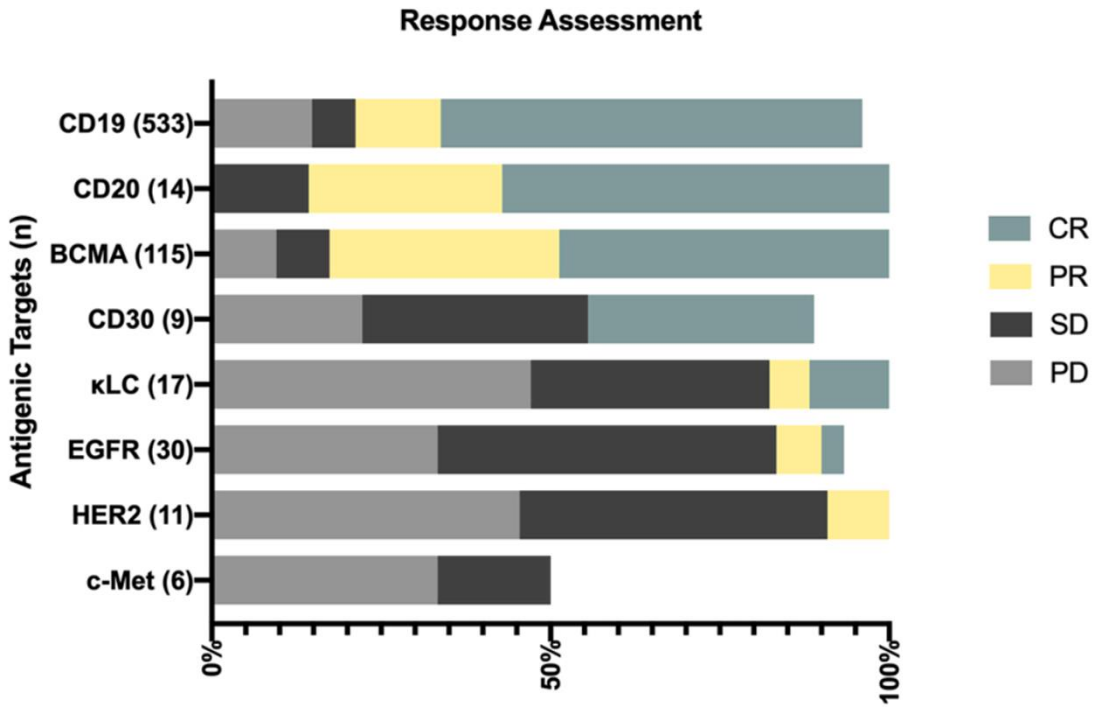


**Fig. 12.** The best response of clinical results in specific antigenic targets.

Moreno-Cortes, E et al. *Critical reviews in oncology/hematology* vol. 159 (2021): 103239.

# CAR T Therapie: Solide Tumoren holen auf

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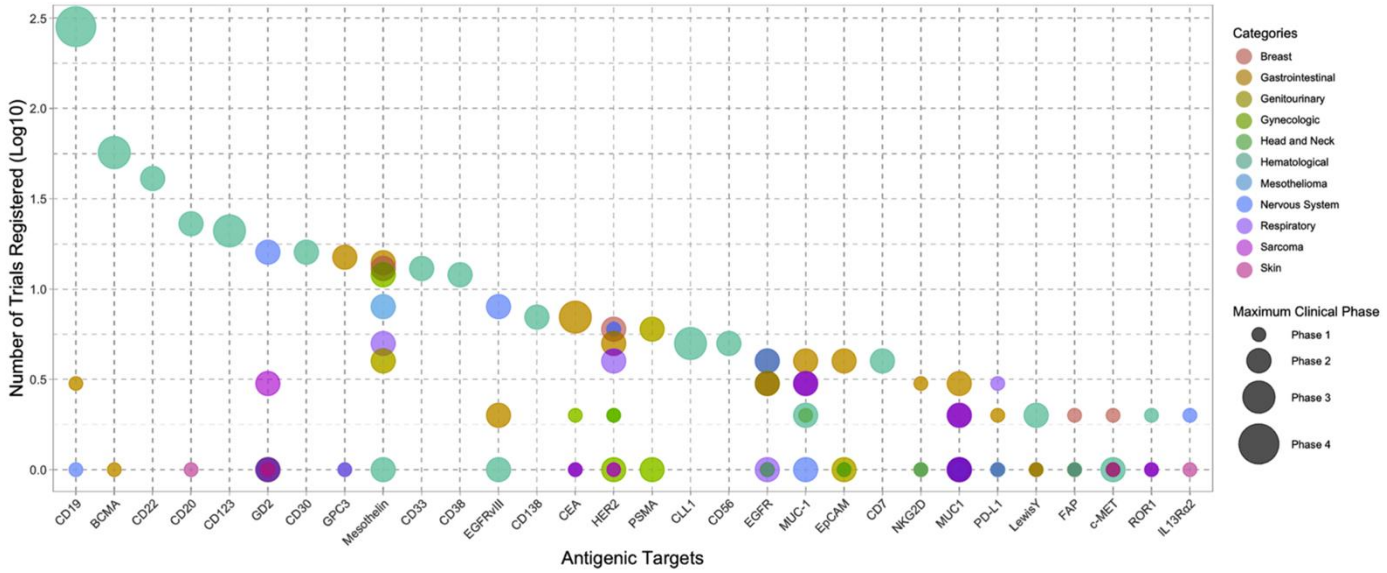


Moreno-Cortes, E et al. *Critical reviews in oncology/hematology* vol. 159 (2021): 103239.

LINDE ACADEMY

# CAR T-Zell Studien: 2 Länder dominieren

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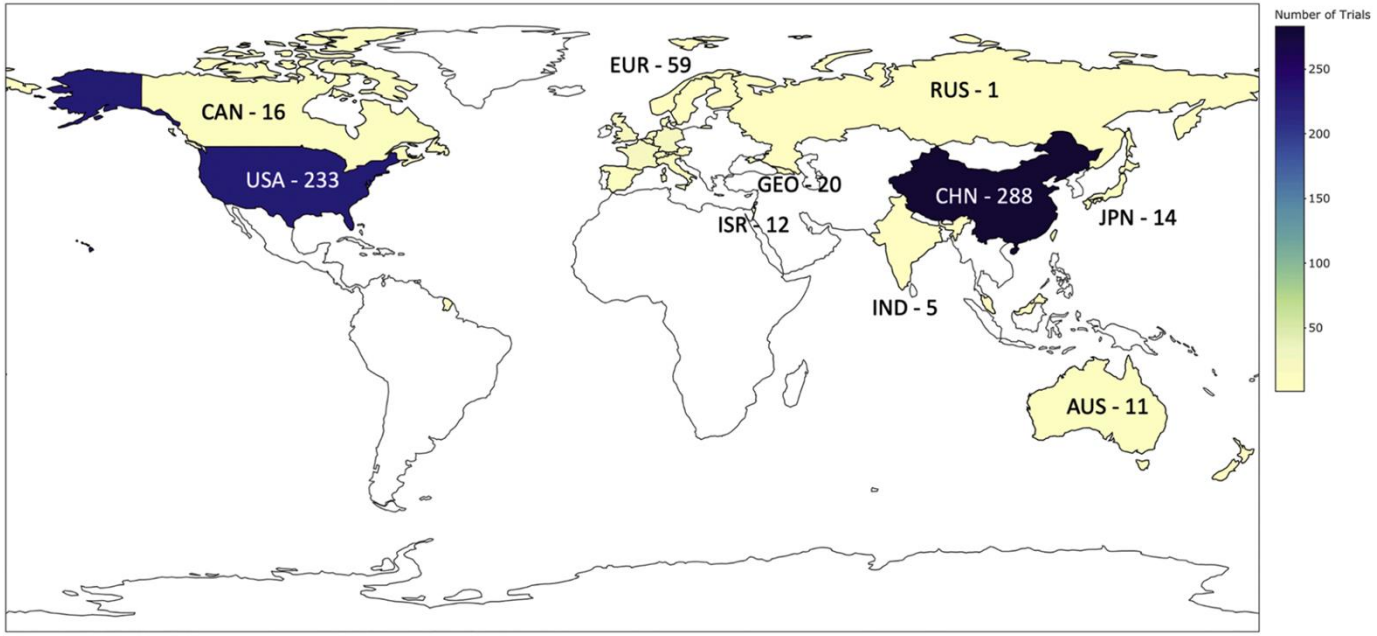


**Fig. 4.** World distribution of CAR T-cell therapy trials registered in ClinicalTrials.gov.

Moreno-Cortes, E et al. *Critical reviews in oncology/hematology* vol. 159 (2021): 103239.

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# CAR T Therapie: Bereits 4. Generation in Entwicklung

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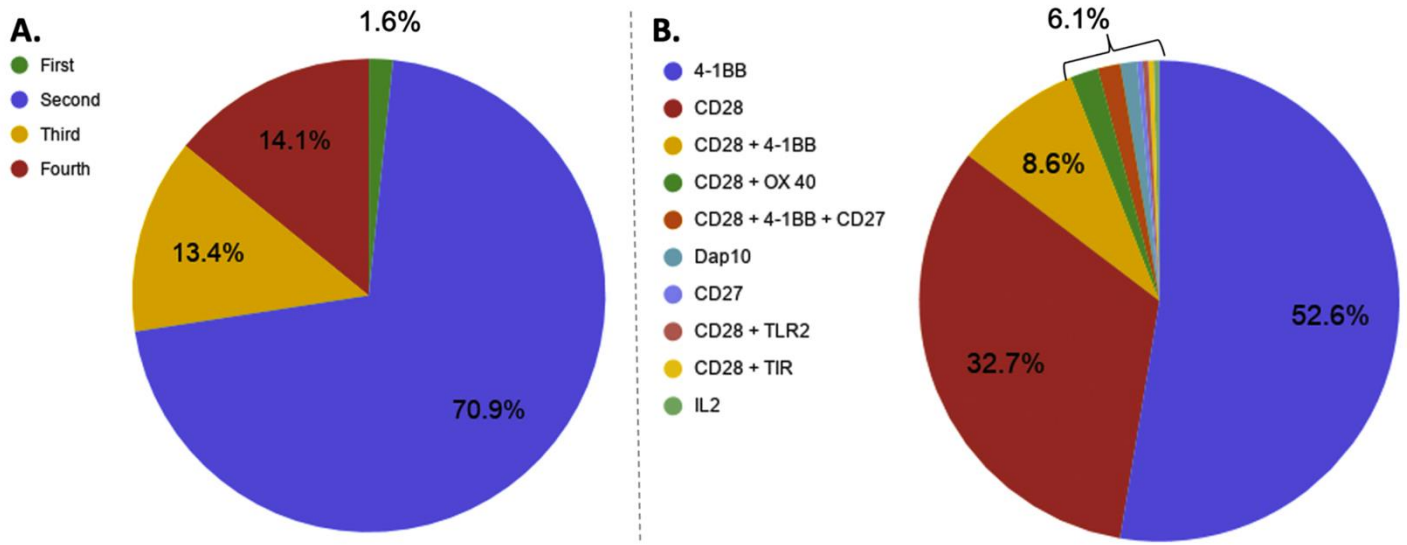


Moreno-Cortes, E et al. *Critical reviews in oncology/hematology* vol. 159 (2021): 103239.

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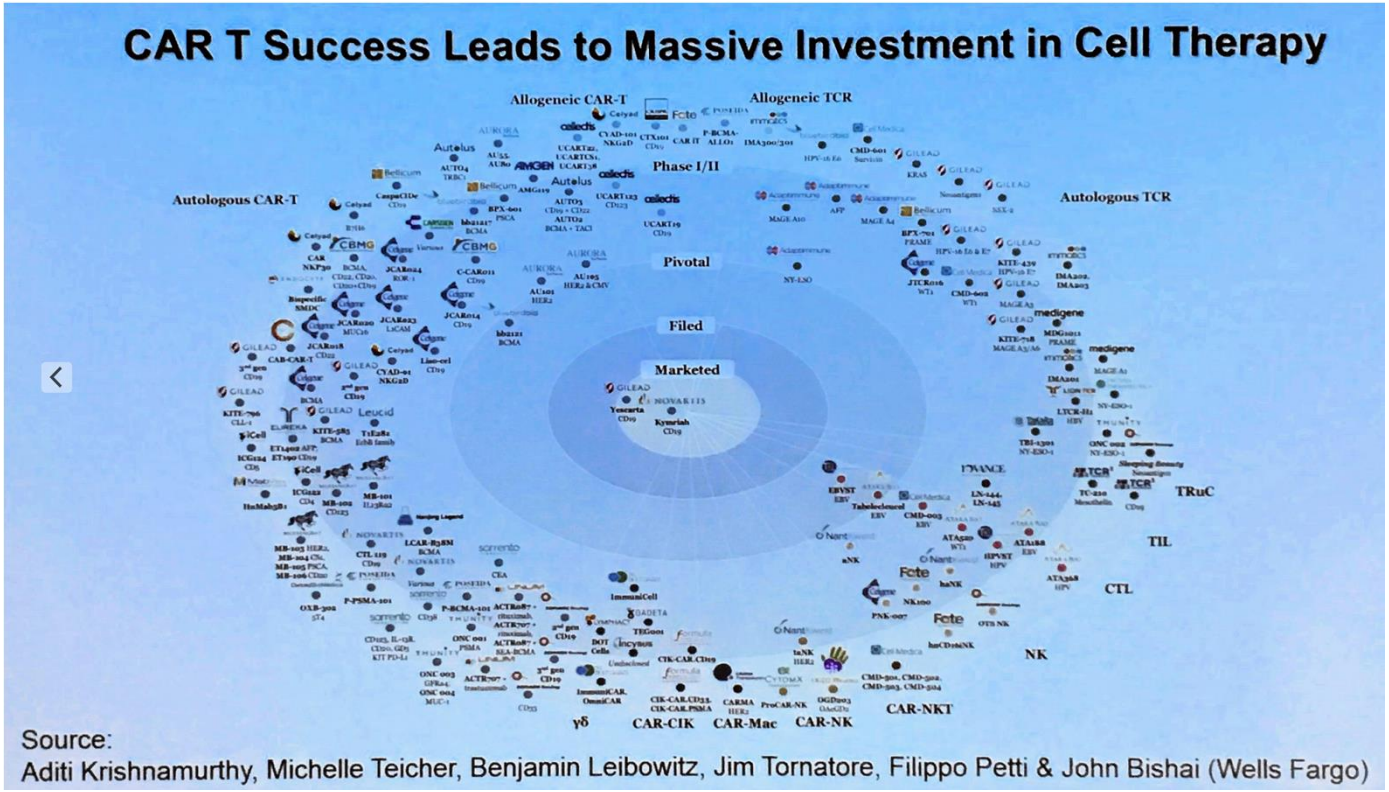
# Kommerzielles Interesse riesig!

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KLINIK LINDE
CLINIQUE DES TILLEULS

LINDE TILLEULS ACADEMY

# Zusammenfassung

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1. Zelltherapien (z.B. CAR T-Zellen) haben bei Lymphomrezidiven einen **fixen** Stellenwert erlangt und können vielleicht Heilung vermitteln
2. CAR T-Zellen werden auch für andere Erkrankungen entwickelt
3. In den USA frühzeitige und zum Teil ambulante Therapie
4. Risiko: Neurologie und *Cytokine release syndrome*!
5. Es ist die Zukunft der Krebstherapie in vielen Bereichen!

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# Ansprechpartner Klinik Hirslanden

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**PD Dr. U. Petrausch**

**Prof. Dr. C. Renner**

**PD Dr. P. Samaras**

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# Danksagung

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1. Projektmanagement/Direktion Klinik Hirslanden
2. Datamanagement/Tumorzentrum Klinik Hirslanden
3. Pflege/Sekretariat Onkozentrum Hirslanden
4. Stationäre Pflege Klinik Hirslanden
5. Intensivstation
6. Apotheke
7. Zentrallabor Zürich
8. Notfallzentrum
9. Neurozentrum
10. Klinik für Innere Medizin
11. Ärzte Onkozentrum Hirslanden & Zürich bzw. neu „*Klinik für Hämatologie und Onkologie Hirslanden Zürich*“


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# Vielen Dank für Ihre Aufmerksamkeit!

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