Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

13.– 16. Juni 2019

KML-Experten berichten vom EHA 2019 in Amsterdam

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Multiples Myelom

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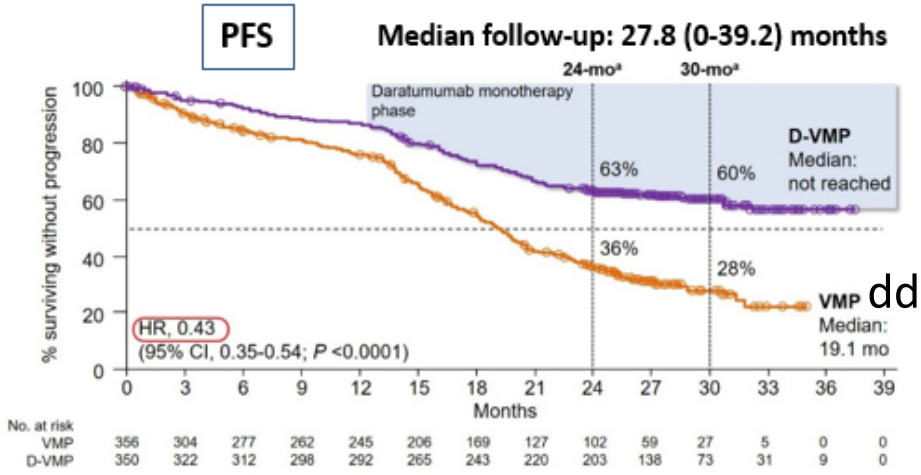
Kapitel 1

Erstlinientherapie

Behandlungsziele bei transplantations-fähigen Patienten mit neu diagnostiziertem Multiplen Myelom

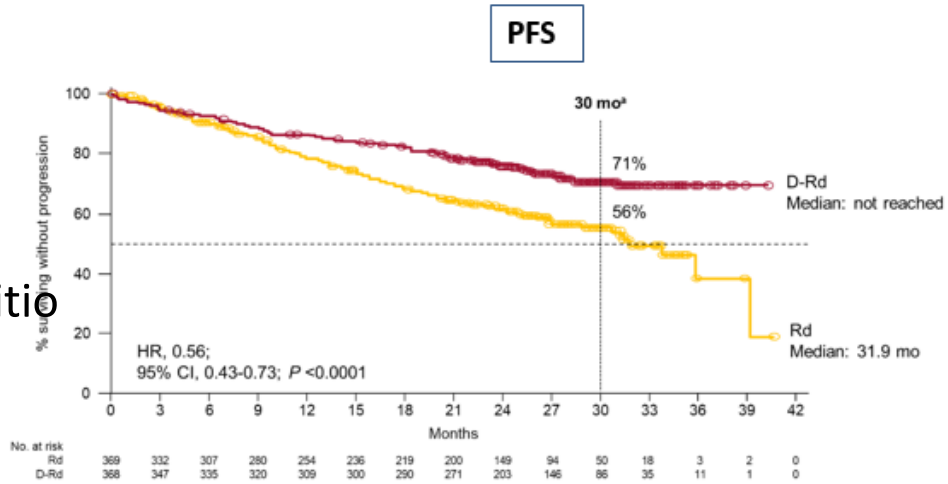
What can we achieve in the NTE patient with NDMM ?

phase III ALCYONE study



Mateos MV et al, N Engl J Med. 2018;378(6):518-528

phase III MAIA study



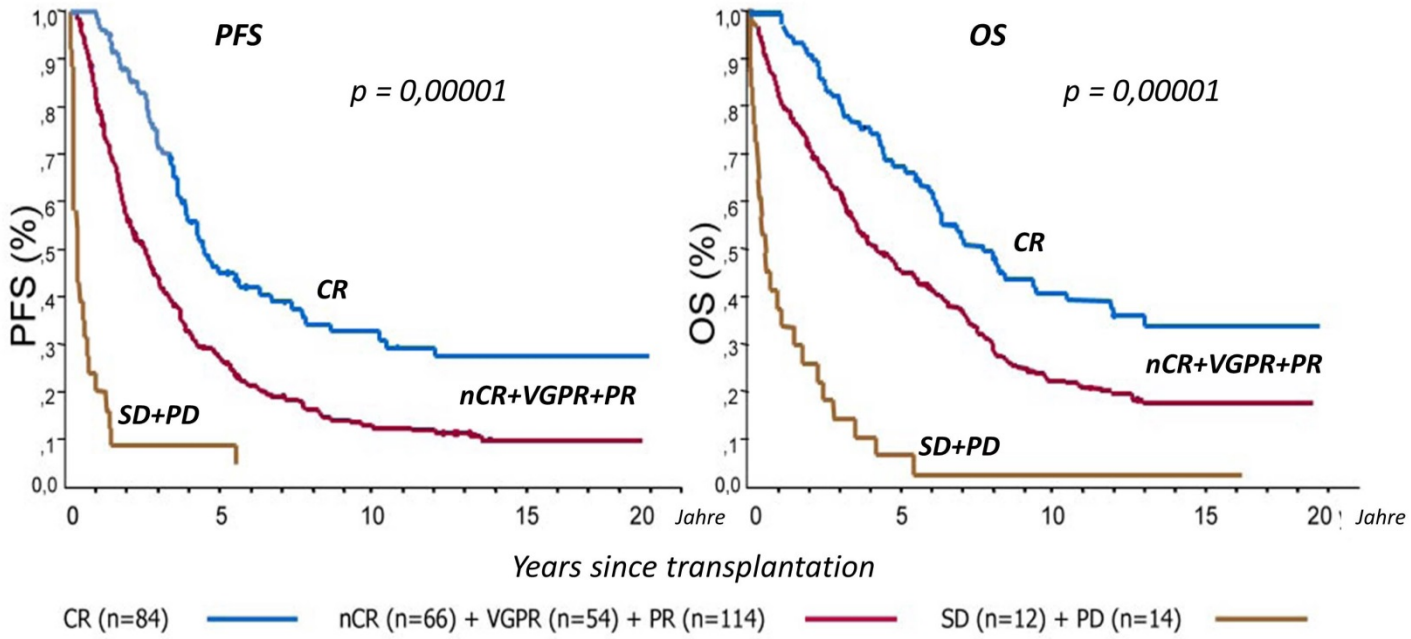
Facon T et al, N Engl J Med. 2019;380(22):2104-2115

- Addition of Monoclonal Antibodies to current doublets/triplets (Rd, VMP, VCP, VRD) → will achieve a PFS of up to 3-4 years !
- Additional lines of therapy will provide another 2 years of PFS !

➡ Limited disease control inspite of novel agents/new concepts!

What can we achieve with current treatment options in NDMM ?
Cure of a subgroup of transplant-eligible patients with MM !

CR vs. nCR/VGPR/PR vs. SD/PD (n = 344)

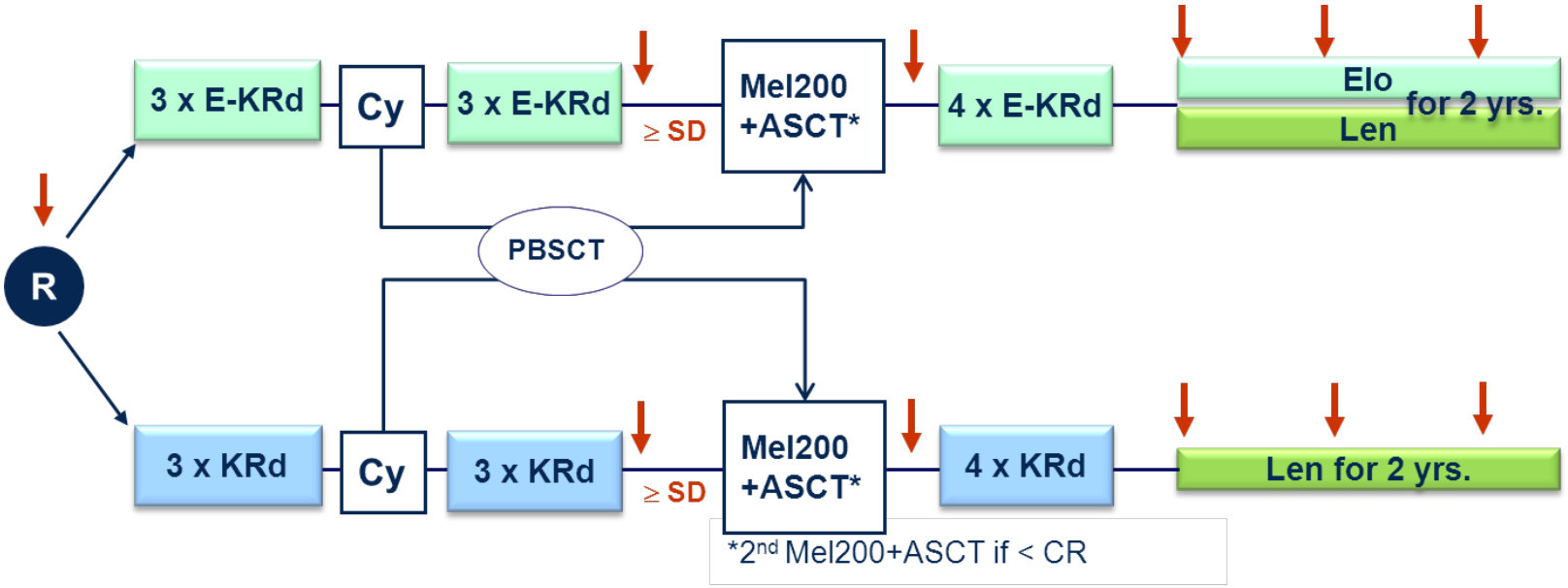


- **Landmark-study: plateau in OS and PFS after 11 years for patients with CR (35%)**
- **Afer 17 years 35 % of the patients alive with CR and 11% of the patients with nCR+VGPR+PR**
- **None of the patients has received novel agents!**

Martinez-Lopez J et al., Blood 2011

4-Drug combinations in induction and consolidation: DSMM XVII Study

55 Centers in Germany, Austria and Switzerland; *n=580*



MRD assessment by flow cytometry

Projected endpoints:

Experimental arm: KRd-Elo SCT KRD-Elo Elo-Len

MRD-negativity EOT: 65%

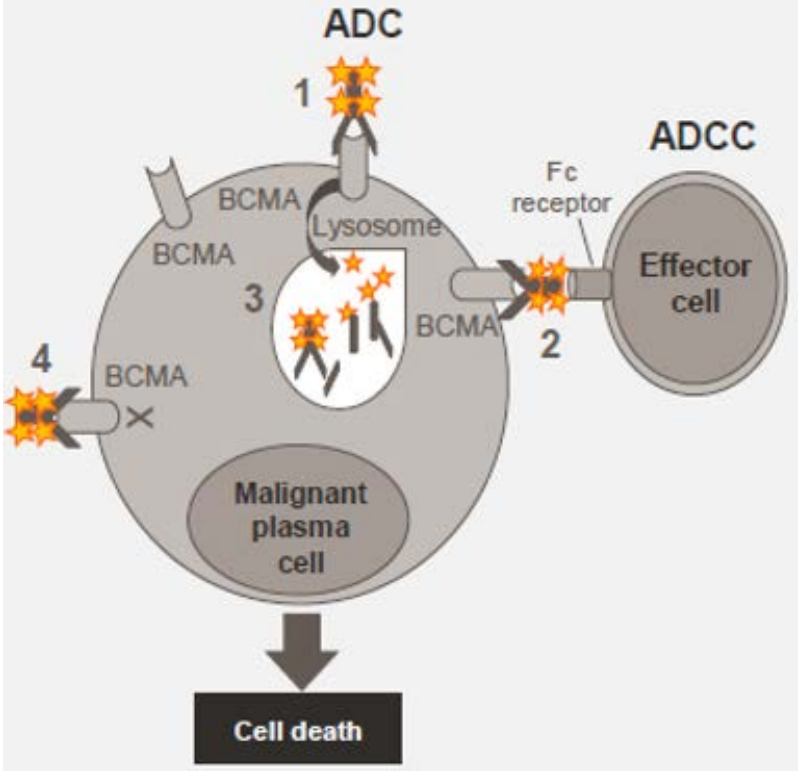
Goal: PFS 10 yrs !!

Background

- BCMA: expressed on differentiated B cells; requisite for long-lived plasma cells' survival
- **BCMA is broadly expressed on malignant plasma cells**
- **GSK2857916:** humanized, afucosylated IgG1 **anti-BCMA antibody;** neutralization of soluble BCMA
  - Preclinical studies demonstrate its selective and potent activity[1]

GSK2857916	
Cytotoxic agent	– MMAF (non-cell permeable, highly potent auristatin
Afucosylation	– Enhanced ADCC
Linker	– Stable in circulation

Four mechanisms of action:
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signaling inhibition



DREAMM-1:
Phase-I-Studie Anti-BCMA Antikörper GSK2857916

Part 1: Dosissteigerung(N=38) Part 2: Expansion (N=35)

Patienten mit RRMM

MM-Patienten: E Linien Vortherapie (Alkylans, PI, IMiD)

Progression innerhalb von 60 Tagen nach der letzten Therapie und messbarer Erkrankung

GSK2857916

Die empfohlene Dosis für Phase 2 beträgt 3,4 mg / kg

GSK2857916
3.4 mg/kg
Q3W, IV 1-Std. Infusion

- Steroid-Augentropfen werden 4 Tage lang mit jeder Infusion verabreicht, um Hornhautereignisse zu mildern

Behandlung bis zu 16 Zyklen oder bis zum Fortschreiten/inakzeptable Toxizität

Trudel S, et al. Presented at ASH 2017; Abstract 741

DREAMM-1 Part 2

Demografische Merkmale und Basismerkmale

Characteristic	Part 2 (N=35)
Age (years), median (min, max)	60 (46–75)
Females/males, %	51/49
≥5 prior lines, n(%)	**20 (57)**
ASCT	31 (89)
IMiDs, n (%) Lenalidomide Pomalidomide Thalidomide Refractory to IMiD	35 (100) 33 (94) 21 (60) 12 (34) 32 (91)
PI, n (%) Bortezomib Carfilzomib Refractory to PI, n (%)	36 (100) 34 (97) 28 (80) 34 (97)
Daratumumab, n (%) Refractory to daratumumab, n (%)	14 (40) 13 (37)
Refractory to IMiD/PI, n (%)	31 (89)
Refractory to IMiD/PI and prior daratumumab, n (%)	**12 (34)**
Cytogenetics risk, n (%) **High risk** **Other (non-high risk, not done, or missing)**	 **10 (29)** **25 (71)**

Disposition und Behandlungsstatus des Patienten

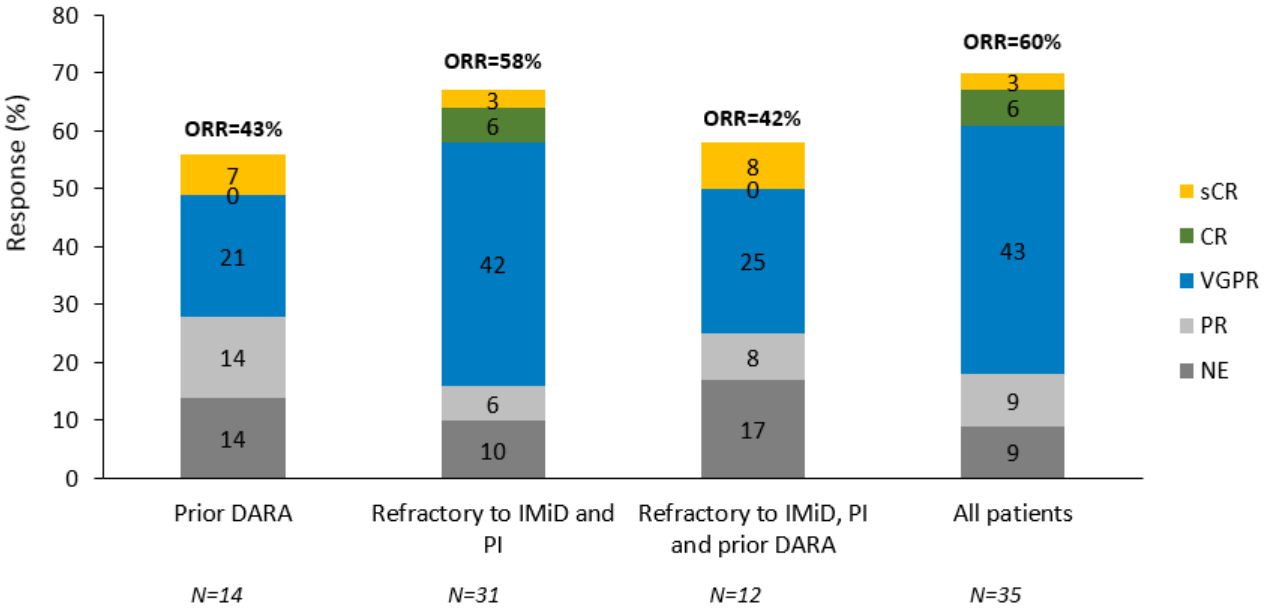
		Part 2 (N=35)
Treatment status	Ongoing, n (%)	17 (49)
	Discontinued study treatment, n (%)	18 (51)
	Reason for discontinuation, n (%): Disease progression Adverse event Decision by subject or proxy Completed scheduled treatment Investigator discretion	 15 (43) 2 (6) 1 (3) 0 0
Exposure	**Median number of treatment cycles (range)**	**5 (1–13)**
Duration of follow-up (months)	Median (range)	6.6 (1–10)

Trudel S, et al. Presented at ASH 2017; Abstract 741

DREAMM-1 Part 2: Wirksamkeit

ORR = 60% (21/35; 95% CI: 42.1%, 76.1%)
•1 sCR, 2 CR, 15 VGPR, 3 PR

Ansprechen



- Medianes PFS 7.9 Monate
- Mittlere Ansprechdauer nicht erreicht

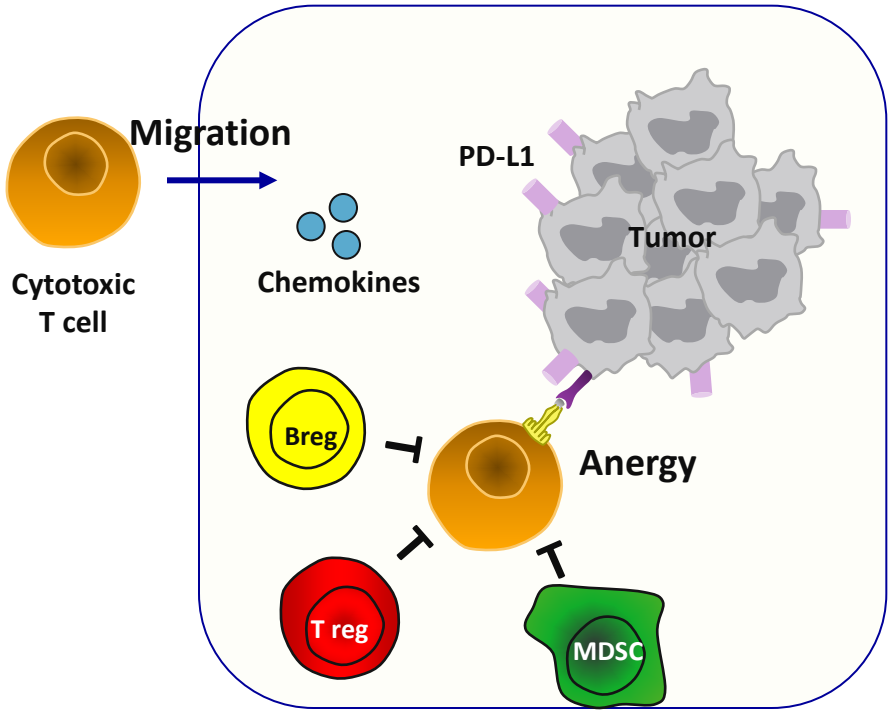
Trudel S, et al. Presented at ASH 2017; Abstract 741

Kapitel 2

Zelluläre Immuntherapie

Hürden & Fallsticke

Zelluläre Immuntherapie: Hurdles and pitfalls

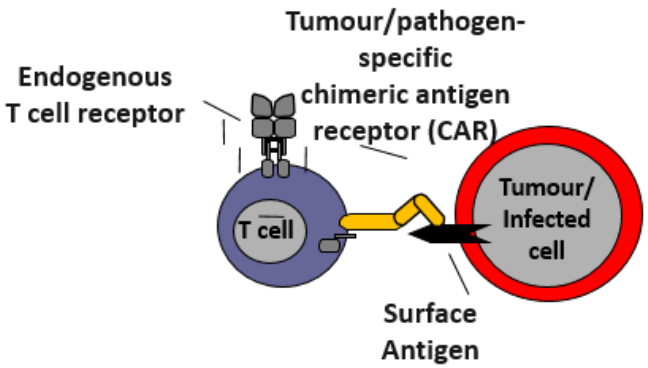


Problem:

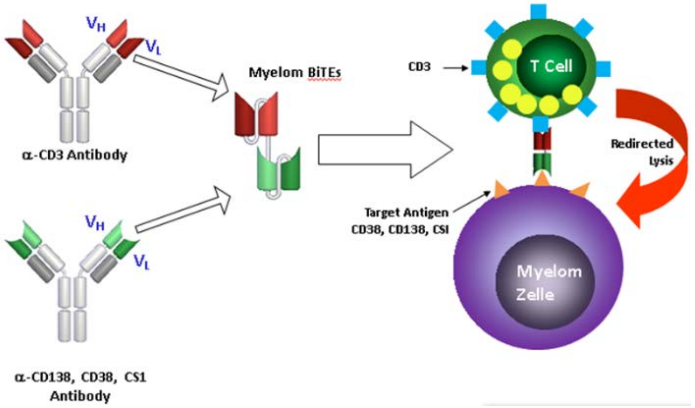
- **Fehlen einer ausreichenden Anzahl tumorspezifischer voll-funktions-fähiger T-Zellen**
- **Rekrutierung von T-Zellen**
  - Hohes Level innate Immunsignale
  - Chemokinexpression
- **Trotzdem dominieren negative Immunregulatoren**
  - Inhibitorische Rezeptoren
  - Suppressive Zellen
  - Suppressive Enzyme (IDO, Arginase)

Gajewski TF, et al. Curr Opin Immunol 2011;23(2):286-92;
Spranger S, and Gajewski TF. J Immunother Cancer 2013;1:16.

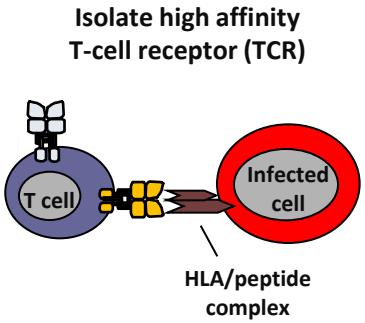
Wie behandelt man Myelom mit autologen T-Zellen? Wie kann man die Frequenz von MM-reaktiven funktionsfähigen T-Zellen erhöhen?



Mit CAR T Zellen



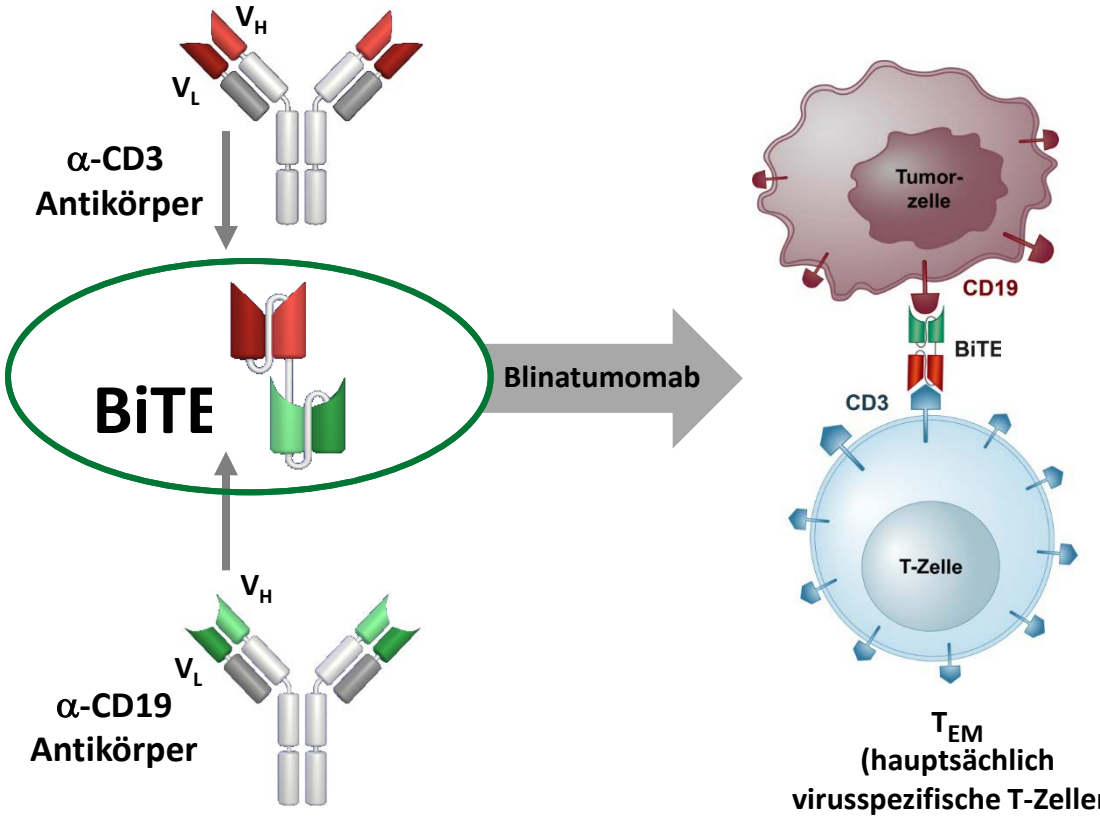
mit BiTEs



mit TCR transduzierte T Zellen

BiTE Moleküle:

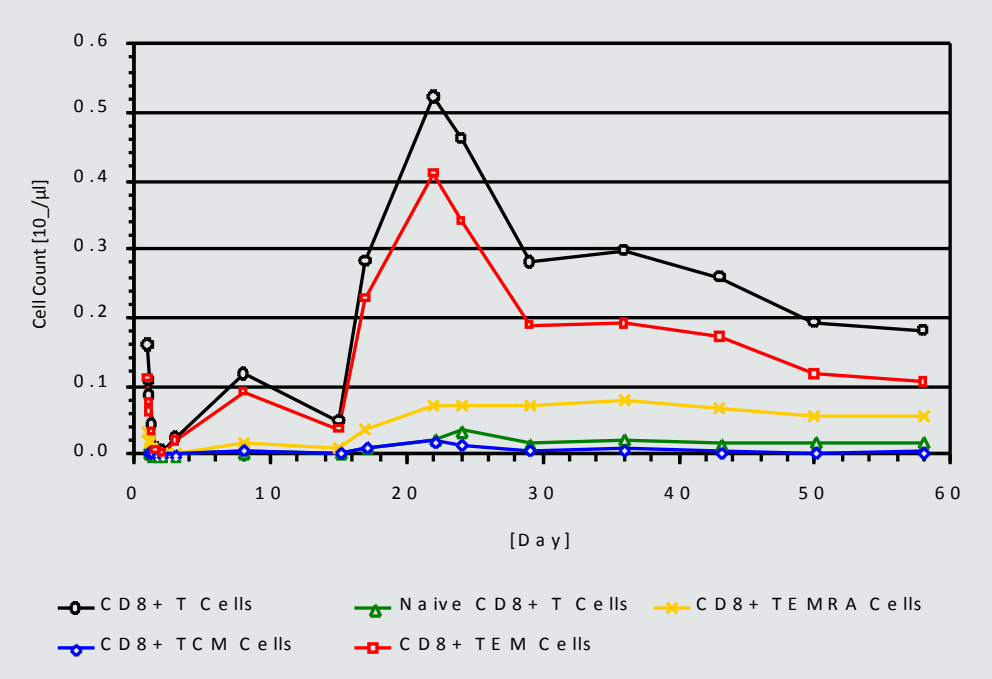
Ziel: Erhöhung der Frequenz tumorreaktiver T-Zellen



Wu J, et al. J Hematol Oncol 2015;8:104

Expansion von Effektor Memory T-Zellen

Oligoklonale Expansion von T-Zellen

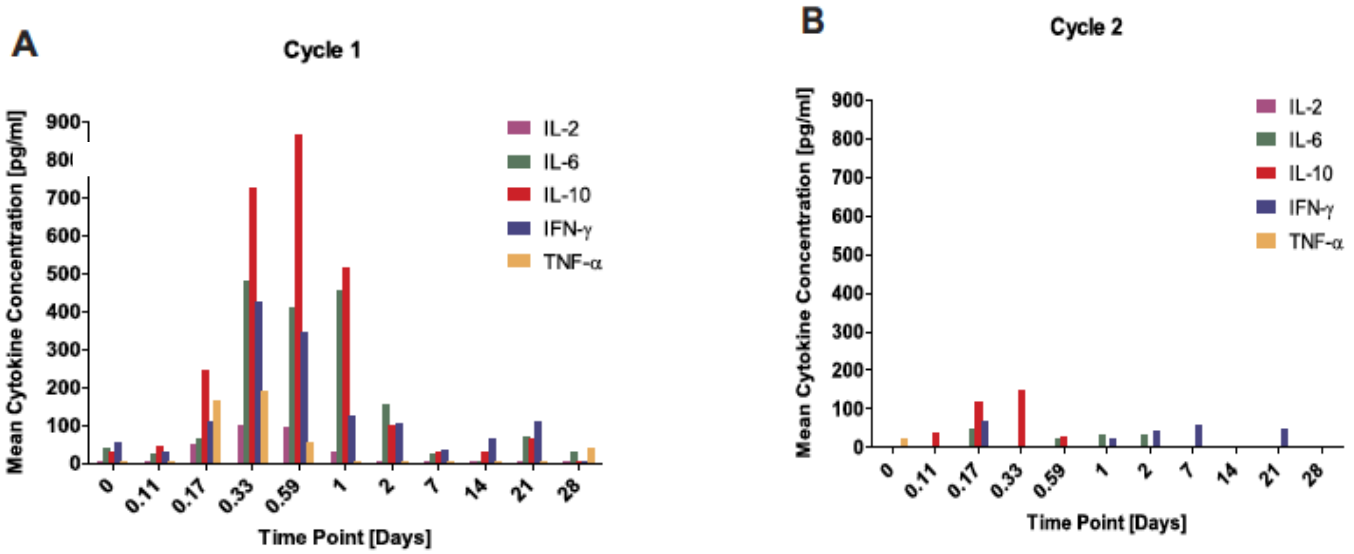


Die Expansion von CD8 + T-Zellen in der 3. Woche der Behandlung mit Blinatumomab um das Dreifache wird dominiert durch die Proliferation der cytotoxischen CD8 + TEM-Untergruppe

Klinger M, et al. Blood 2012;119(26):6226-33.

Toxicity? When?

CRS: Zytokinprofil bei Patienten, die mit BiTEs behandelt wurden (Fieber, Schüttelfrost, Hypotonie usw.)



Klinger M, et al. Blood 2012;119(26):6226-33.

➢ Die meisten unerwünschten Ereignisse traten innerhalb von 72 Stunden nach Beginn der Behandlung auf und nahmen danach stark ab

➡ Nach der Infusion von CAR T-Zellen kann ein CRS bis zu 16 Tage nach der Infusion auftreten und mehrere Tage bis Wochen anhalten

CNS Adverse Events

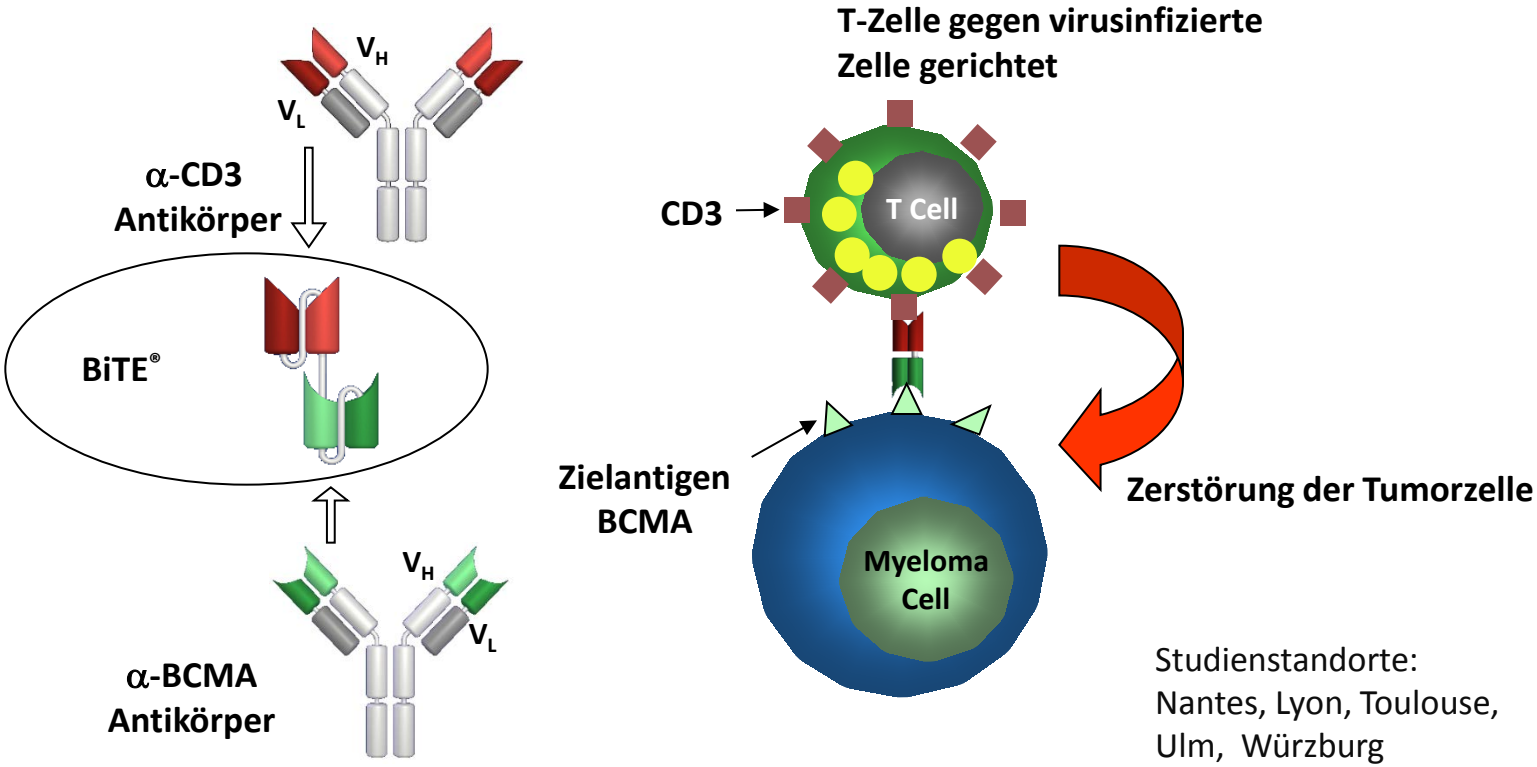
15 patients	All AE Grade ≥3 (N = 70)	
Preferred Term	n	%
Encephalopathy	6	8.6
Aphasia	3	4.3
Headache	2	2.9
Tremor	2	2.9
Disorientation	2	2.9
Speech disorder	1	1.4
Coordination abnormal	1	1.4
Cerebellar syndrome	1	1.4
Transient ischemic attack	1	1.4
Paresis	1	1.4
Seizure	1	1.4
Dysarthria	1	1.4
Hallucination	1	1.4
Emotional distress	1	1.4
Grand mal	1	1.4

Goebeler ME et al, J Clin Oncol. 2016

- Die klinisch relevantesten Nebenwirkungen waren vollständig reversible ZNS-Ereignisse
- Diese Form der Neurotoxizität ist auf CD19-gerichtete bispezifische Antikörper beschränkt!
- Keine andere Spezifität (z. B. CD20, BCMA, PSMA, EpCAM, CEA, EGFR usw.) zeigte Neurotoxizität!

Bei CAR-T-Zellen ist die Neurotoxizität auch mit einer CD19-Spezifität am ausgeprägtesten. Es wurde jedoch auch berichtet, dass die Anwendung von CAR-T-Zellen mit unterschiedlicher Spezifität eine gewisse Neurotoxizität induziert

BiTE®-Moleküle sind kleine bi-spezifische Antikörper



Studienstandorte:
Nantes, Lyon, Toulouse,
Ulm, Würzburg

Topp MS, et al. ASH 2018; Abstract 1010

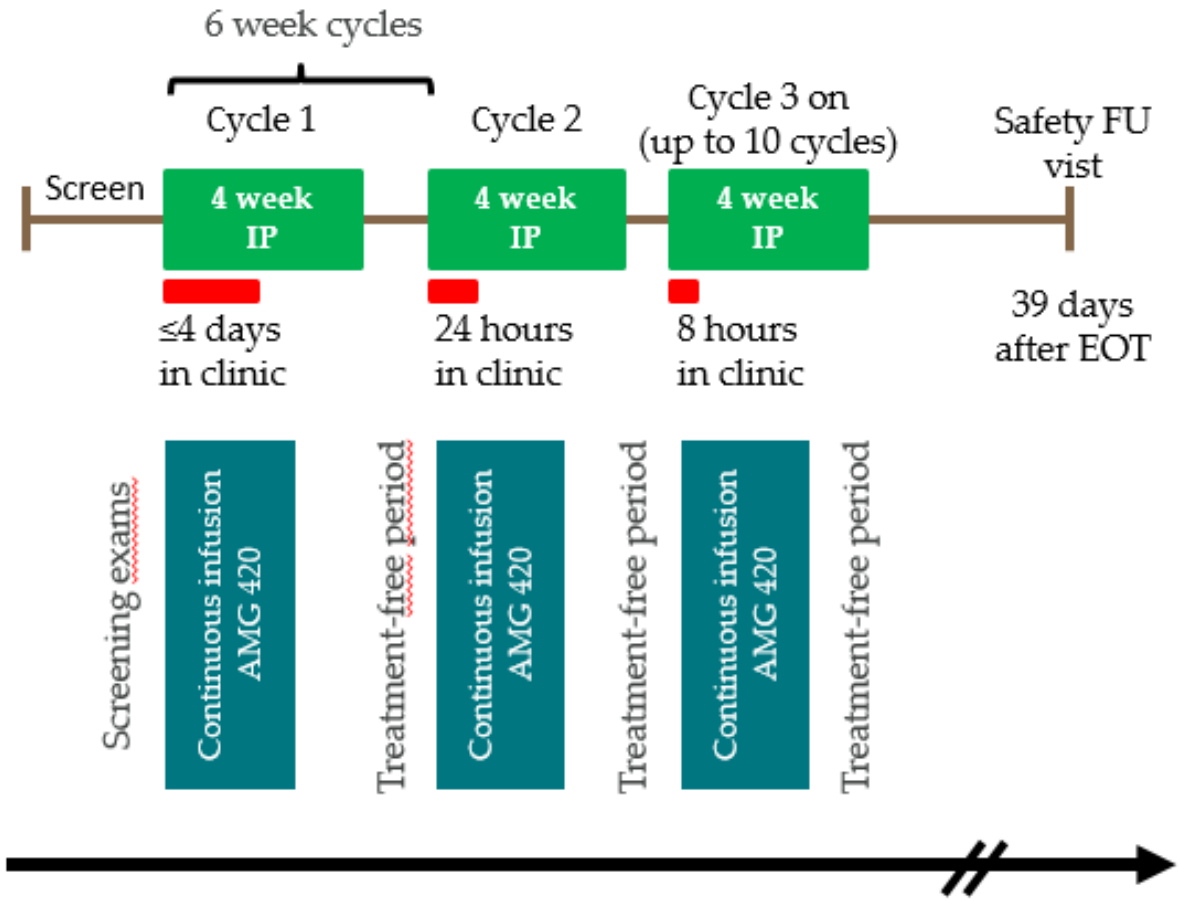
AMG 420, an anti-BCMA BiTE, induces MRD-negative CRs in RRMM patients: results of a dose escalation FIH phase 1 study

- Median of 4 prior lines; 26% exposed to either dara or elo; 31% double refractory to both PIs and IMiDs
- Up to 10 cycles of AMG 420: MTD was 400 µg/d with DLT observed with 800 µg/day (CRS grade 2), and PNP (reversible with high dose IV IgG)
- 2 fatal opportunistic infections (IA, adenovirus) occurring late after the administration of AMG 420

Topp MS, et al. ASH 2018; Abstract 1010.

Trial sites: Nantes, Lille, Toulouse, Ulm, Würzburg
BCMA, B cell maturation antigen; BiTE, bispecific T cell engager; CR, complete response; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; FIH, first in human; IgG, immunoglobulin G; IMiD, immunomodulatory drugs; IV, intravenous; MRD, minimal residual disease; MTD, maximum tolerated dose; PI, proteasome inhibitor; PNP, peripheral neuropathy; RRMM, relapsed/refractory multiple myeloma.

Studienschema



*NCT02514239.
EOT, end of treatment; FU, follow-up; IP, investigational product.

Topp MS, et al. ASH 2018; Abstract 1010

AMG 420: Updated results of a FIH Phase 1 dose escalation study

Safety

	N=42
SAEs, n (%)	21 (50%)
SAEs in ≥2 patients, n (%) Infections Peripheral polyneuropathy	12 (29%) 2 (5%) 2 (5%)
Treatment-related SAEs, n (%) Peripheral polyneuropathy Oedema	 2 (5%) 1 (2%)
Grade 2/3 CRS	3 (7%)
Death*	4 (9%)

*2 deaths from AEs (acute respiratory distress from flu / aspergillosis; fulminant hepatitis related to adenovirus infection); neither treatment-related.

- 18 SAEs required hospitalisation
- No anti-AMG 420 antibodies were detected

- Data cut of Dec 10, 2018
- 42 patients received AMG 420 (0.2-800 µg/d)
- 800 µg/d was determined to not be tolerable as 2/3 patients had DLTs
  - 1 case of grade 3 CRS and 1 case of grade 3 polyneuropathy; both required hospitalisation and subsequently resolved
- 400 µg/d established as recommended dose for further investigation

Topp MS, et al. EHA 2019; Abstract S825.

Responding patients characteristics

# prior lines[1]	BL BM PC%[2]	Dose µg/d × # cycles	Months of treatment	Best response
4 incl SCT×2	10	6.5 × 10	13.7	C8V1: CR
3 incl SCT×2	2	50 × 10	13.6	C3-C10: PR
3 incl SCT	2	100 × 7	9	C4-C5: CR
6 incl Dara	6	200 × 4	5.2	C3: MRD^{neg} sCR
3 incl SCTx2	3	400 × 4	4.6†	C3: MRD^{neg} sCR
4 incl SCT×2	25	400 × 7	10.2†	C3: MRD^{neg} sCR
6 incl SCT×2	60	400 × 7	9.0†	C1: MRD^{neg} sCR
2 incl SCT×2	80	400 × 6	8.8†	C1: MRD^{neg} sCR
4 incl SCT, Dara	80	400 × 1	1.0	End C1: PR
5 incl SCT×3	28	800 × 2, then 400 × 1	3.3	C2, C3: VGPR
5 incl SCTx2, Dara	0.2	800 × 1	0.5	C1: PR

[1]Overall for the study, daratumumab treatment was reported for 12/42 patients (29%). [2]By morphology. †Still on study; months of treatment as of last reported dose. Only patients with data available at datacut are included. All responders were white.
BL, baseline; BM, bone marrow; CR, complete response; Dara, daratumumab; MRD, minimal residual disease; PC, plasma cell; PR, partial response; sCR, stringent complete response; SCT, stem cell transplant; VGPR, very good partial response.

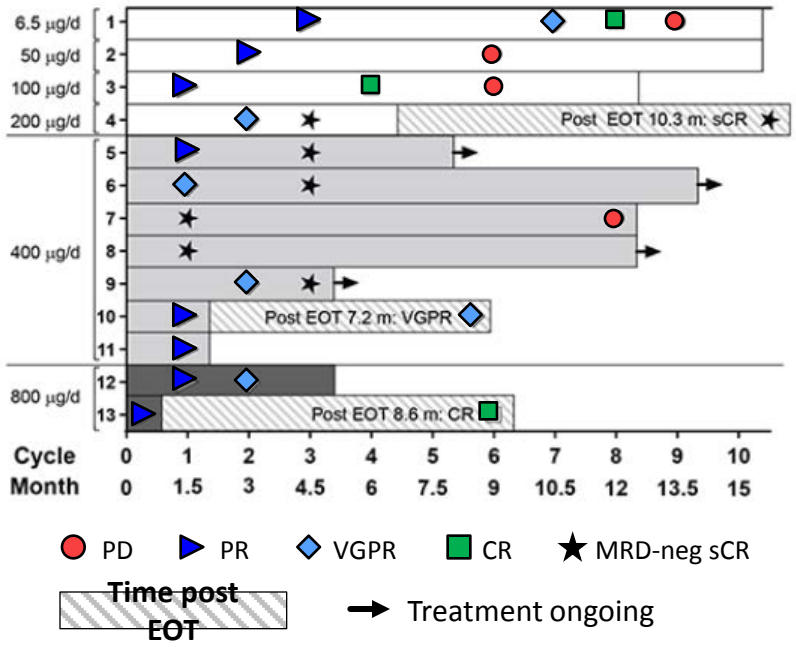
Topp MS, et al. ASH 2018; Abstract 1010.

AMG 420: Updated results of a FIH Phase 1 dose escalation study

Efficacy

- Responses
  - *Overall*: 6 sCRs, 3 CRs, 2 VGPRs, 2 PRs
  - *At 400 µg/d:* 70% response rate
    - 5 MRD-negative sCRs, 1 VGPR, and 1 PR
- Median time to any response: 1 month, with 9 of 13 patients responding in the first cycle
- Duration of response: 5.6-10.4 months
- 4 patients ongoing on treatment
- As of Feb 2019, some responses lasted > 1 year

Patients with RRMM responding to AMG 420 as of Feb 2019



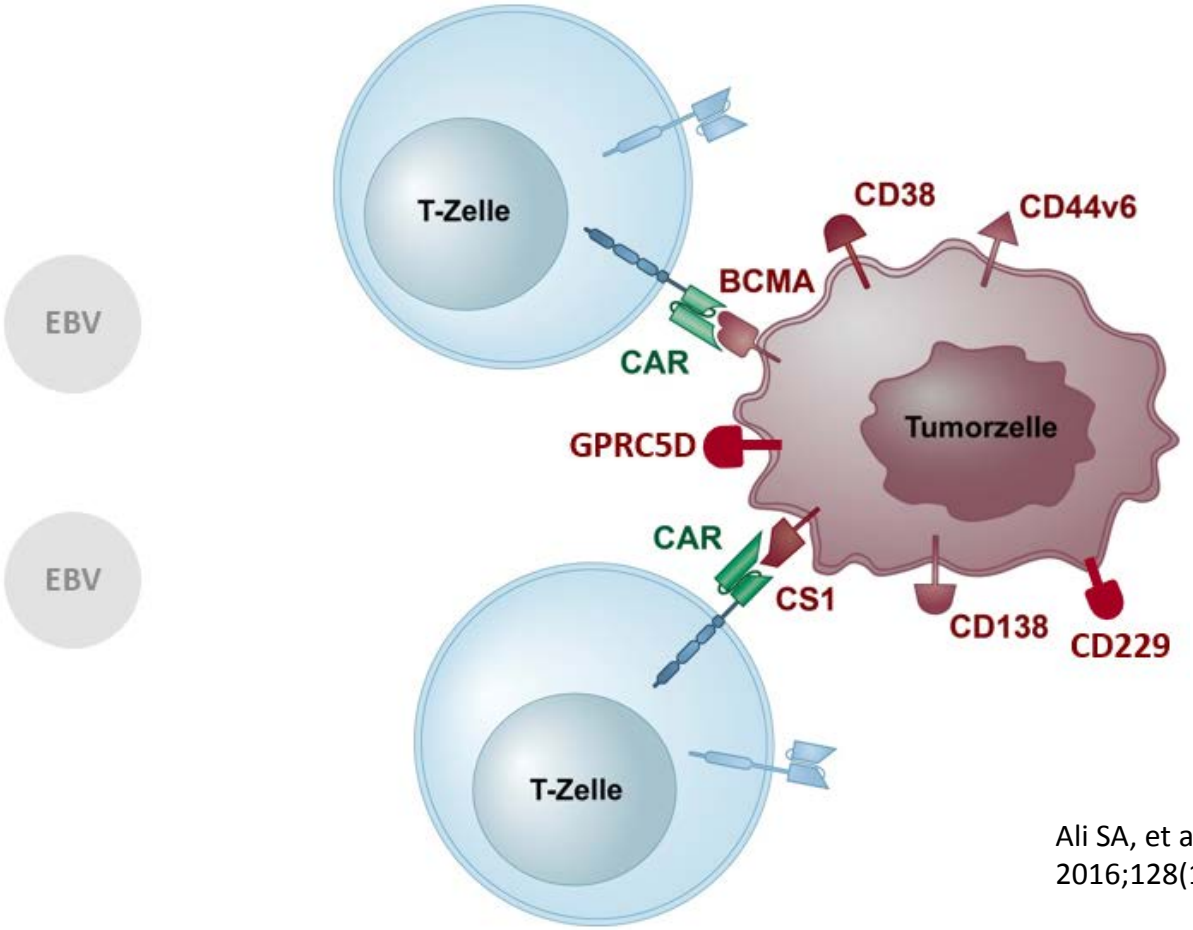
Topp MS, et al. EHA 2019; Abstract S825.

Kapitel 3

CAR-T-Zellen

Personalisierte Immuntherapie - Autologe, genmodifizierte T-Zellen töten die Tumorzellen

Personalized immunotherapy - Autologous gene-modified T cells kill the tumor cell: CAR T cells



Ali SA, et al. Blood 2016;128(13):1688-700.

Bb2121- Trial BCMA CAR T Cells: Demografische Basisdaten und klinische Merkmale

Parameter	Escalation (N=21)	Expansion (N=22)
Median (min, max) follow-up, d	345 (46, 638)	87 (29, 184)
Median (min, max) age, y	58 (37, 74)	65 (44, 75)
Men, n (%)	13 (62)	16 (73)
Median (min, max) time since diagnosis, y	4 (1, 16)	6 (1, 36)
ECOG PS,[a] n (%)		
0	10 (48)	6 (27)
1	11 (52)	16 (72)
High-risk cytogenetics, n (%)		
del(17p), t(4;14), t(14;16)	**8 (38)**	**9 (41)**

Data cutoff: March 29, 2018.
[a]Data at screening presented.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Raje N, et al. ASCO 2018; Abstract 8007

Vorbehandlungen

	Escalation (N=21)	Expansion (N=22)
Median (min, max) prior regimens	**7 (3, 14)**	**8 (3, 23)**
Prior autologous SCT, n (%)	21 (100)	19 (86)
0	0	3 (14)
1	15 (71)	14 (64)
>1	6 (29)	5 (23)

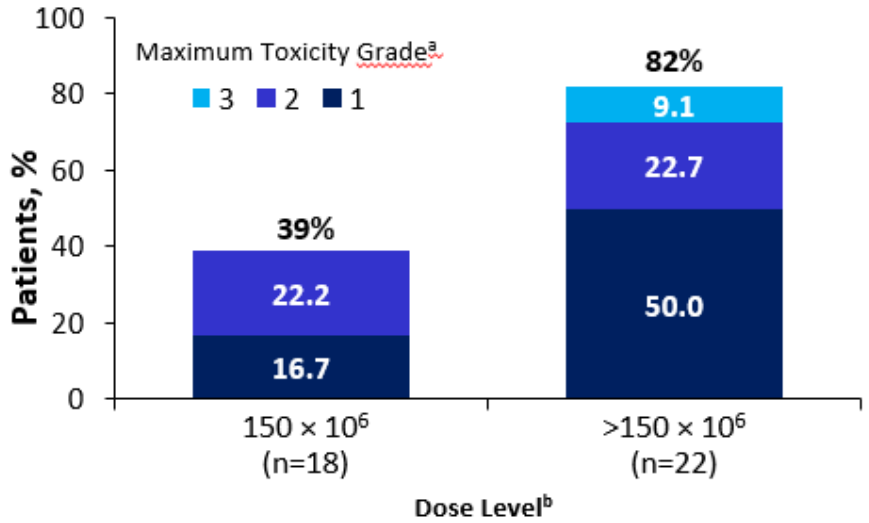
	Escalation (N=21)		Expansion (N=22)	
	Exposed	Refractory	Exposed	Refractory
Prior therapies, n (%)				
Bortezomib	21 (100)	14 (67)	22 (100)	16 (73)
Carfilzomib	19 (91)	12 (57)	21 (96)	14 (64)
Lenalidomide	21 (100)	19 (91)	22 (100)	18 (82)
Pomalidomide	19 (91)	15 (71)	22 (100)	21 (96)
Daratumumab	15 (71)	10 (48)	22 (100)	19 (86)
Exposed/Refractory, n (%)				
Bort/Len	21 (100)	14 (67)	22 (100)	14 (64)
Bort/Len/Car/Pom/Dara	15 (71)	6 (29)	21 (96)	7 (32)

Raje N, et al. ASCO 2018; Abstract 8007

Cytokine release syndrome: Mostly low grade and manageable

Cytokine Release Syndrome Parameters	
Parameter	**Dosed Patients (N=43)**
Patients with a CRS event, n (%)	27 (63)
Maximum CRS grade[a]	
None	16 (37)
1	16 (37)
2	9 (21)
3	2 (5)
4	0
Median (min, max) time to onset, day	2 (1, 25)
Median (min, max) duration, d	6 (1, 32)
Tocilizumab use, n (%)	9 (21)
Corticosteroid use, n (%)	4 (9)

Cytokine Release Syndrome By Dose Level

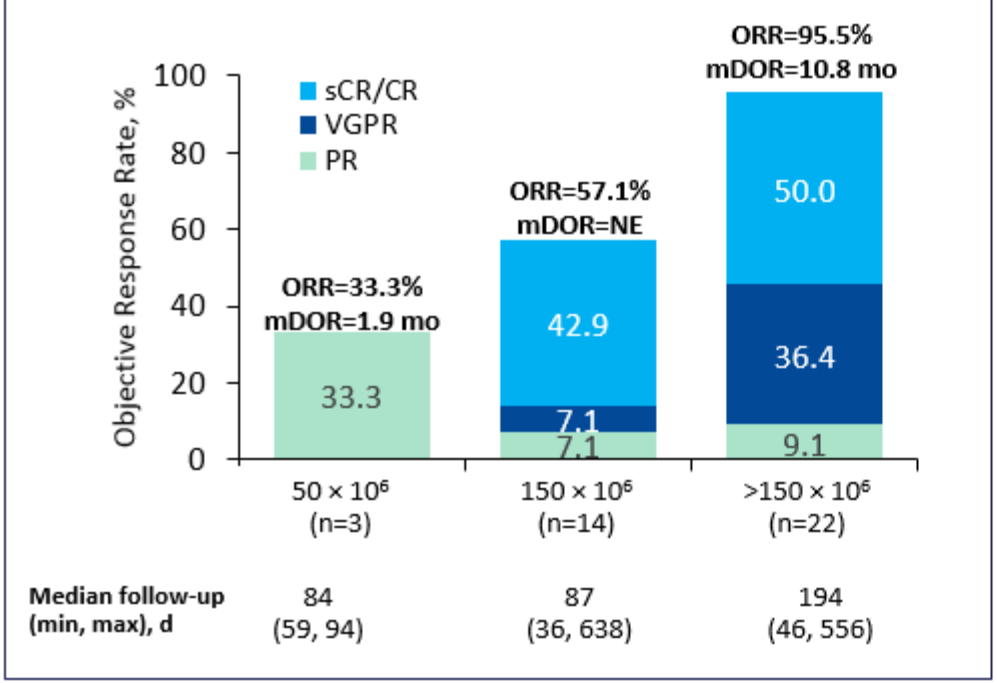


Raje N, et al. ASCO 2018; Abstract 8007

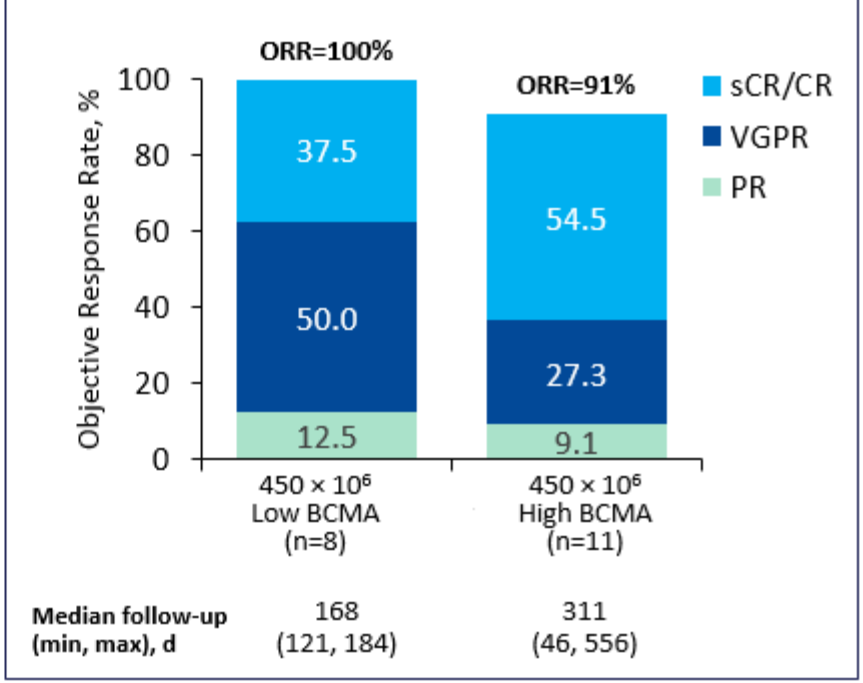
Data cutoff: March 29, 2018. [a]CRS uniformly graded according to Lee DW, et al. *Blood.* 2014;124(2):188-195. [b]3 patients were treated at the 50 x 10^6 dose level for a total of 43 patients.

Response: Dosisabhängig; unabhängig von der BCMA-Expression des Tumors

Tumor Response By Dose[a]



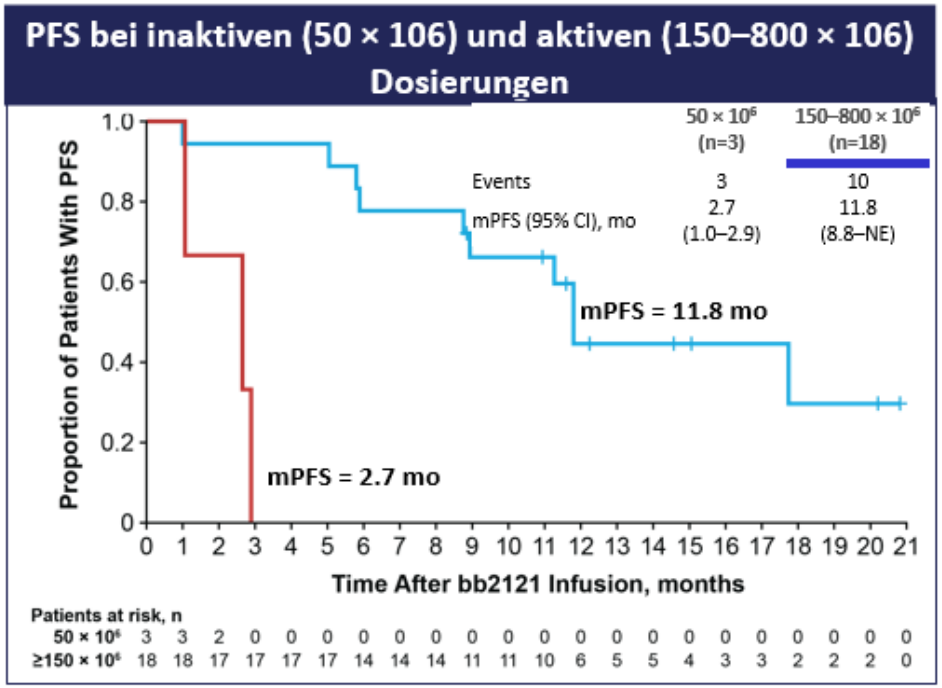
Tumor Response By BCMA Expression[a]

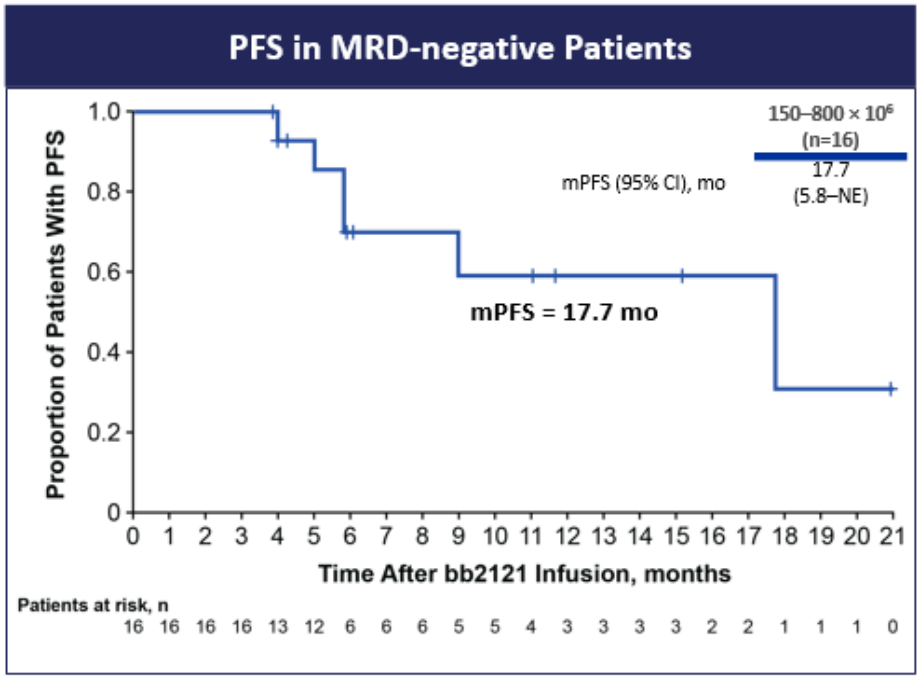


Data cutoff: March 29, 2018. [a]Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.

Raje N, et al. ASCO 2018; Abstract 8007

Progressionsfreies Überleben





Raje N, et al. ASCO 2018; Abstract 8007

Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. [a]PFS in dose escalation cohort.

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

Problem: limited persistence of CAR T cells !

Table S10. CAR T Cell Persistence Over Time.

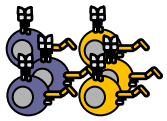
	Month 1	Month 3	Month 6	Month 12
No. at risk	24	22	23	10
No. (%) with detectable vector	23 (96)	19 (86)	13 (57)	2 (20)

All 33 patients were included in the analysis. Data from samples with <50 ng total DNA input were excluded.

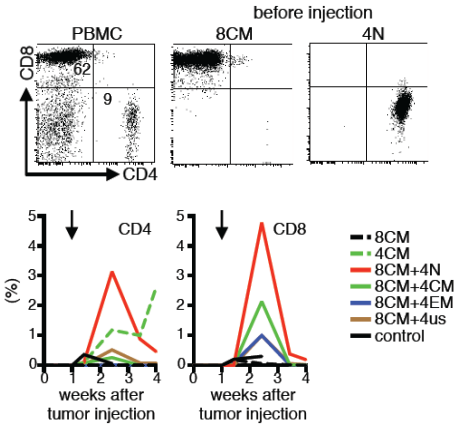
Raje N et al. N Engl J Med 2019; 380(18):1726-1737

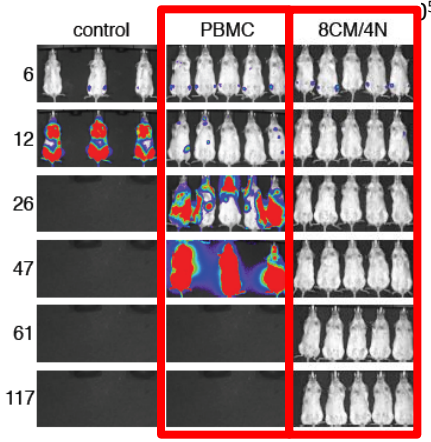
Defined composition of the CAR T-Cell-Product

CAR T cells from PBMC
- random composition
- total dose: $8x10^5$



CAR T cells from defined subsets
- 1:1 ratio of $CD8T_{CM}$:$CD4T_N$
- $8x10^5$

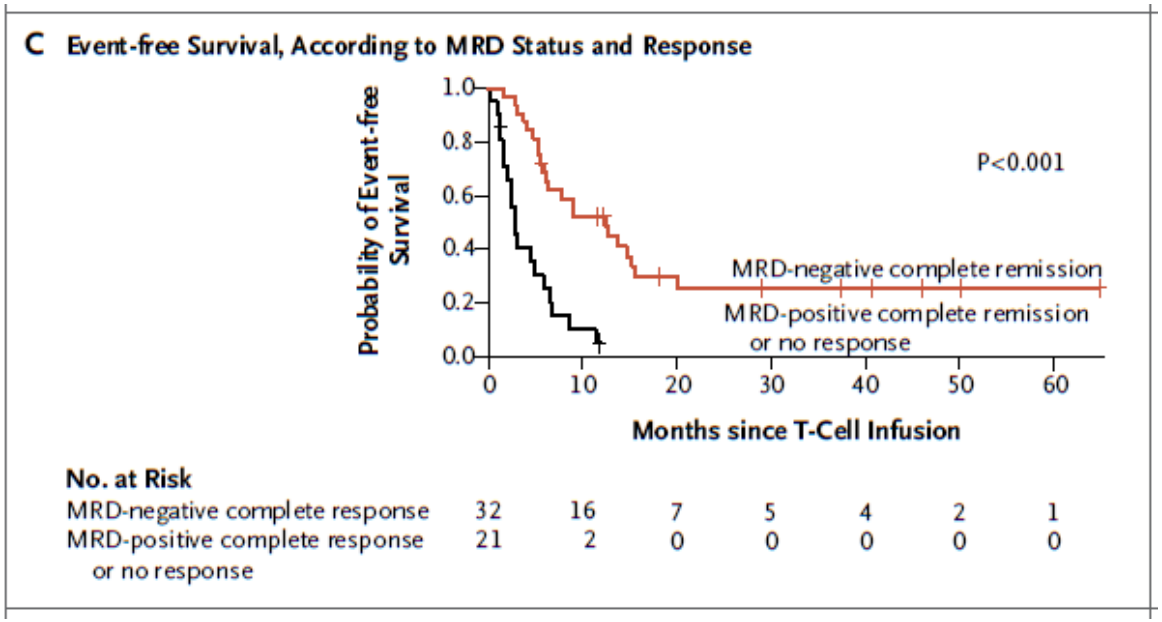




Sommermeyer & Hudecek et al. , Leukemia 2016

→ CAR T cells with defined composition as "living drug": increased safety, effectiveness and consistency

When should CAR T Cell /Bite Therapy be performed?
Long-term disease control following CAR T cell therapy for r/r B-ALL



Park JH et al. New Engl J Med 2018

➡ Long-term disease control only in a minority of patients (often plus allo SCT)
CAR T cell therapy/bispecific antibodies are best placed to eradicate residual disease in a front line setting/ Early relapse setting !

Die Kurzpräsentationen sind online unter

www.lymphome.de/eha2019

Für den Inhalt verantwortlich:

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