Kompetenznetz Maligne Lymphome
Multiples Myelom

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Zusammenfassung

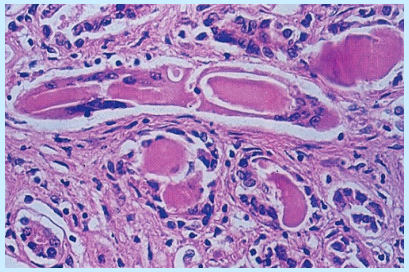
Derzeit - noch ohne die neuen zielgerichteten Therapien und vor Immuntherapien - beträgt das mittlere Überleben eines Myelompatienten (Therapiestart vor 10 Jahren!)

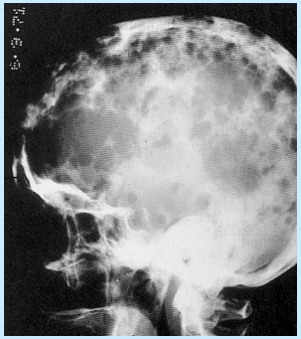
- Nicht für Transplantation geeignet: 7 Jahre!
- Für Transplantation geeignet: 12 Jahre!

➡ Die neuen zielgerichteten Therapien, v.a. die neuen Immuntherapien werden das Überleben und die Heilungschancen bereits in der nahen Zukunft noch weiter verbessern!

Behandlungsentscheidungen beim Multiplen Myelom?
CRAB-Kriterien

Serum Calcium increased	Renal Insuffizienz	Anemia	Bone destruction



Oder:> 2 Bakt. Infektionen / Jahr; Amyloidose; Hyperviskosität

Aktualisierte IMWG-Kriterien: Diagnose des multiplen Myeloms

MGUS	Smouldering Myeloma	Multiple Myeloma
• M Protein < 3 g/dL • klonale Plasmazellen im KM < 10% • Kein myelomdefinierendes Ereignis	• M Protein ≥ 3 g/dL (Serum) oder ≥ 500 mg/24 h (Urin) • Klonale Plasmazellen im KM ≥ 10% - 60% • Kein myelomdefinierendes Ereignis	• Plasmazell-Erkrankung • UND 1 oder mehr myelomdef. Ereignisse • ≥ 1 CRAB* Merkmal

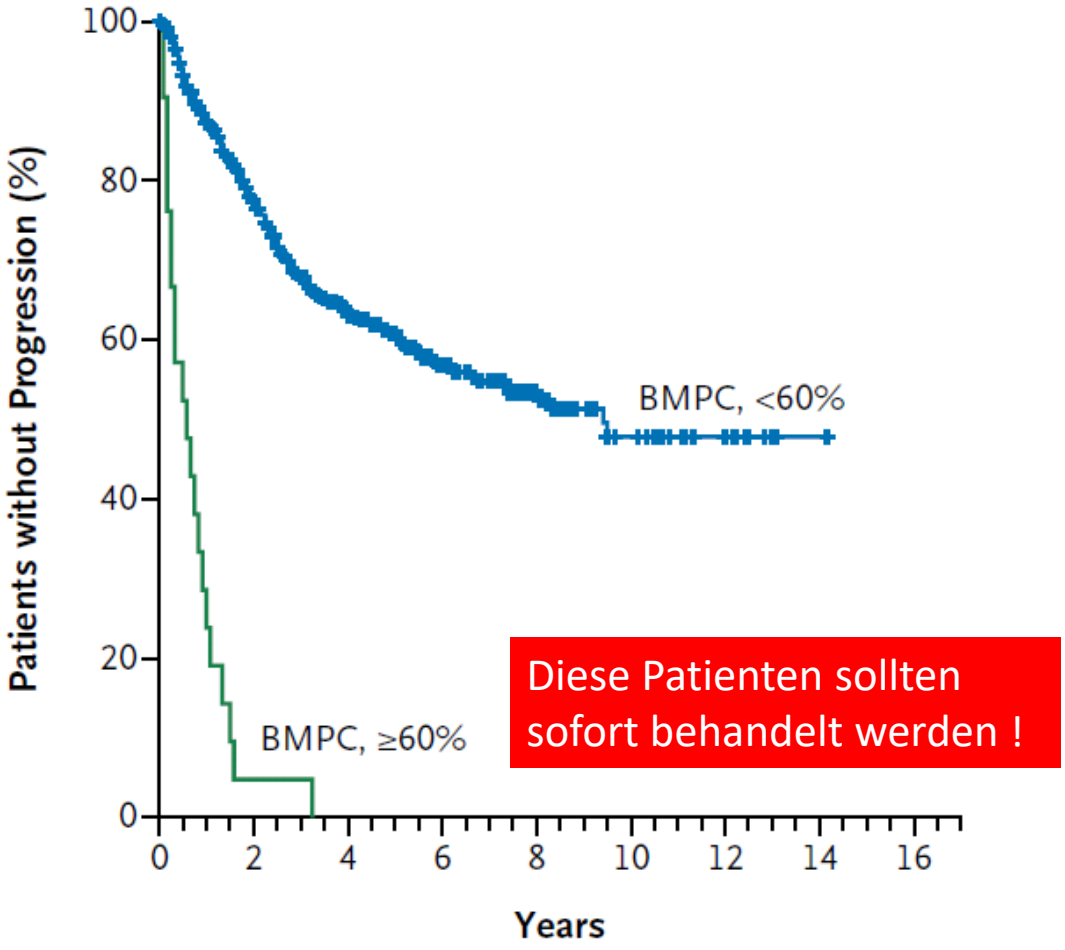
SLiM-CRAB-Kriterien:

- **klonale Plasmazellen im KM ≥ 60%**
- **Freie Leichtketten ratio ≥ 100**
- **>1 fokale Läsion (MRI)**

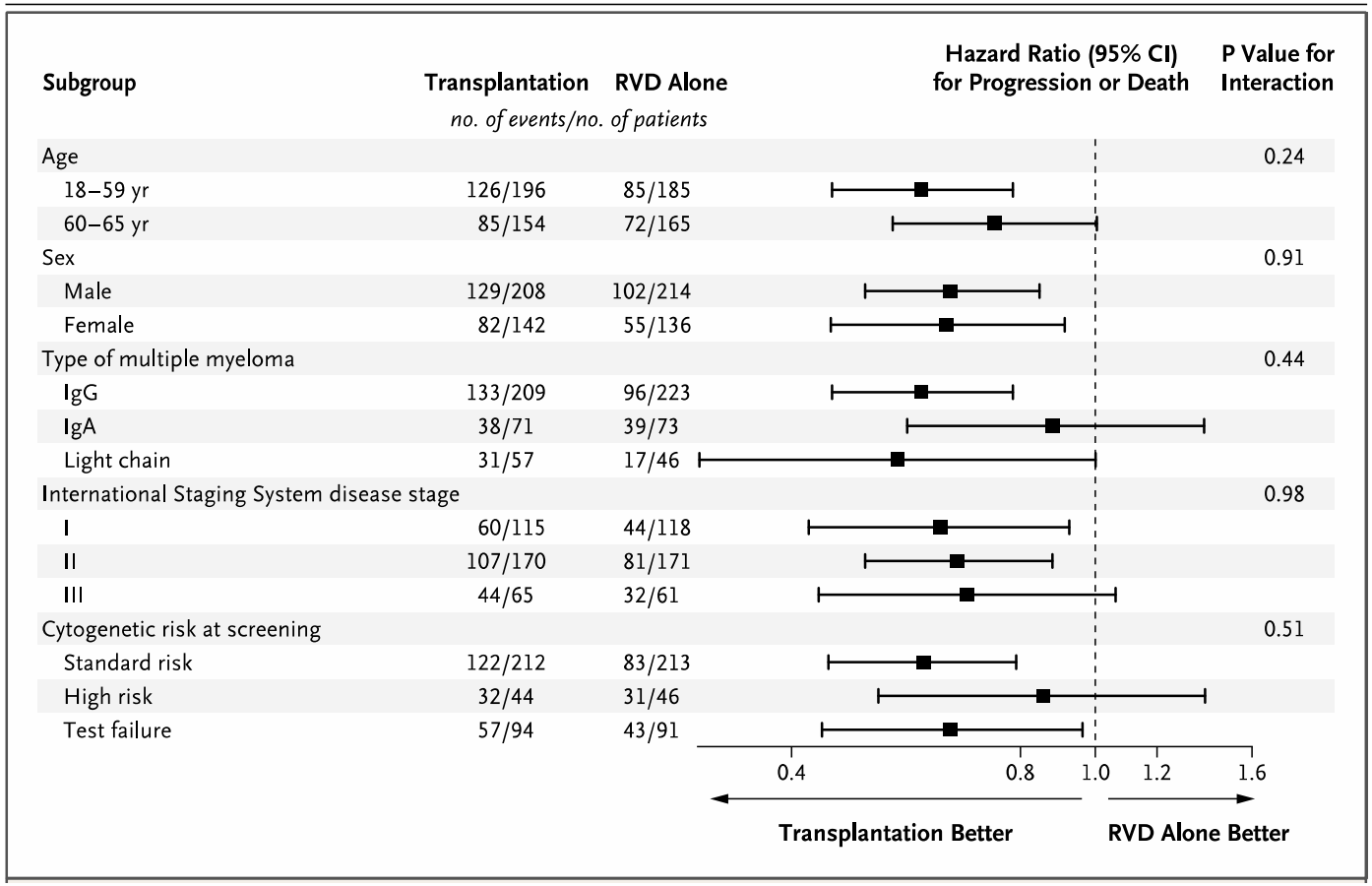
- C: Kalzium (> 11 mg / dL oder> 1 mg / dL höher als ULN)
- R: Niereninsuffizienz (Kreatinin-Clearance <40 ml / min oder Serumkreatinin> 2 mg / dL)
- A: Anämie (Hb < 10 g / dl oder 2 g / dl <normal)
- B: Knochenbefall (≥ 1 lytische Läsionen – konventionelles Röntgen, CT oder PET-CT)

Rajkumar SV, Lancet Oncol 2014

Patienten mit SMM: Behandlung bei Vorliegen der SLiM-Kriterien
Zeit zum Progress in Abhängigkeit von der KM-Infiltration durch MM



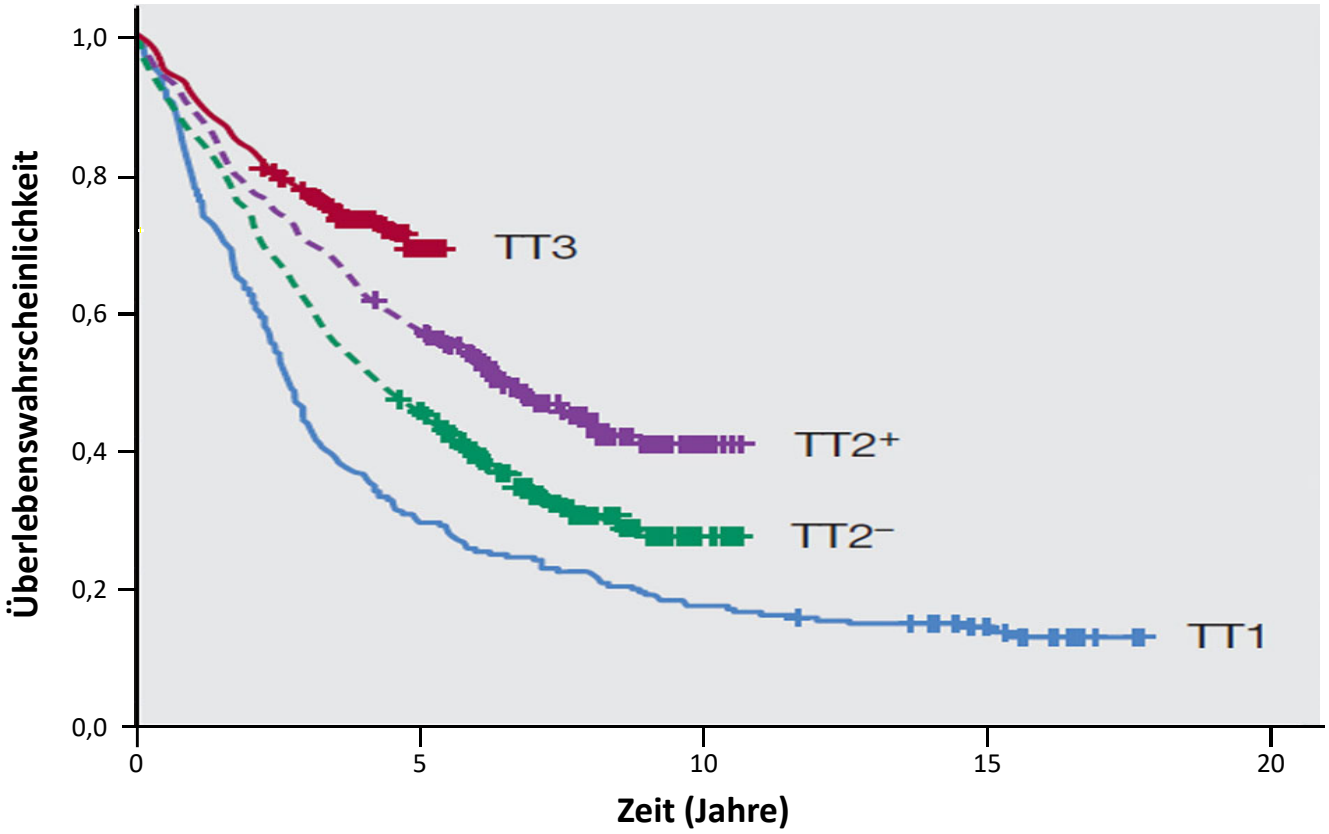
Therapie des jüngeren/transplantations-fähigen Patienten (≤ 70-75 Jahre)
IFM 2009: Vorteil der Hochdosis-Therapie bei allen Subgruppen



Attal et al, NEJM 2017

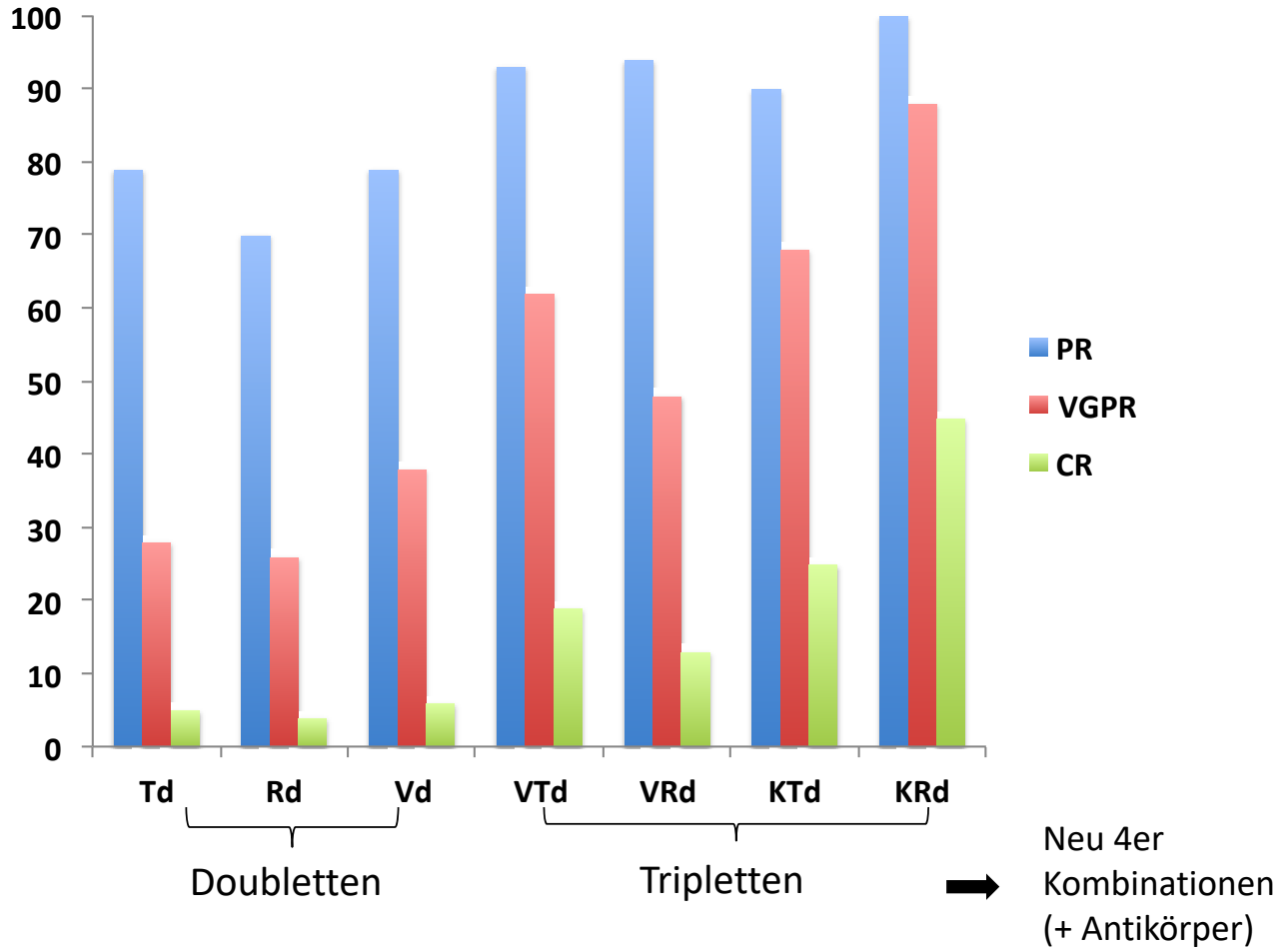
→ 5 Studien mit >3.000 Patienten zeigen Vorteil der HD-Therapie + ASZT (vs konventionelle Therapie)

Zugabe von neuen Substanzen zur Hochdosistherapie und autologen SZT Verbesserung der PFS / Heilungsrate?



Megan O, Barlogie B et al. Clinical Cancer Research 2012

Ansprechraten neuer Induktionstherapien



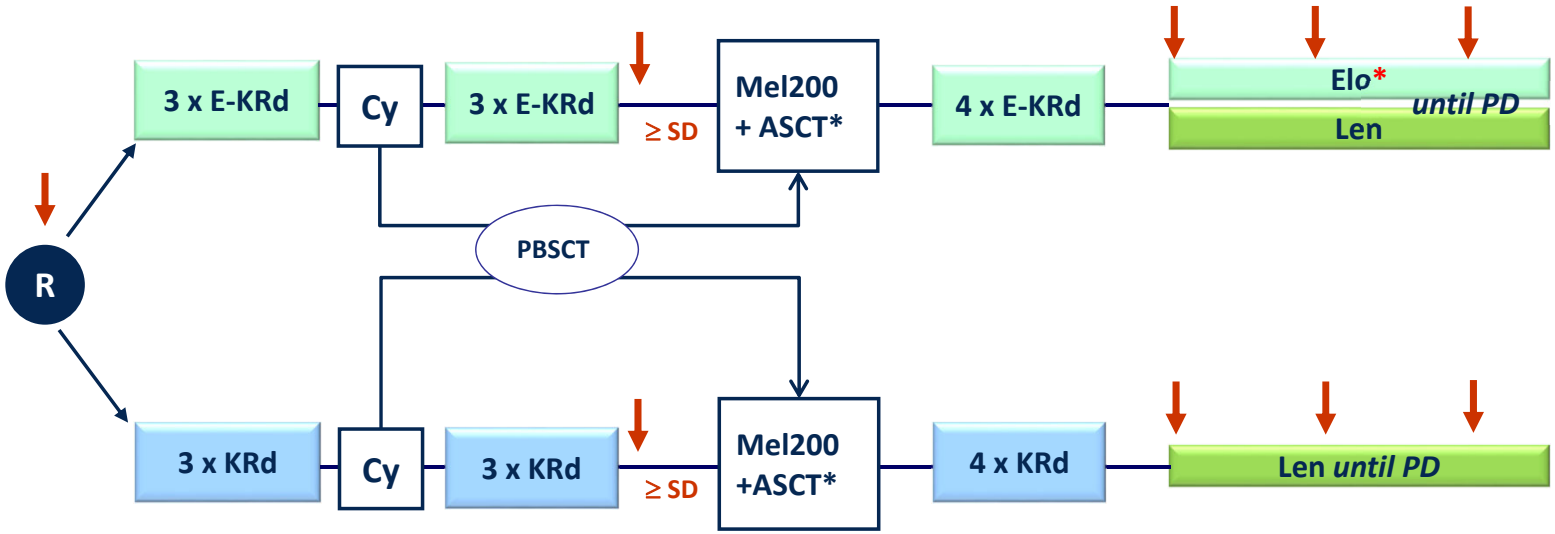
3-er Kombination: Standard bei der Induktionstherapie
Zweit-Generationssubstanzen verbessern die Remissionsqualität

deutsche studiengruppe
multiples myelom

dsmm
doing studies on multiple myeloma

DSMM XVII Studie

55 Zentren in Deutschland, Österreich und Schweiz; *n=576*

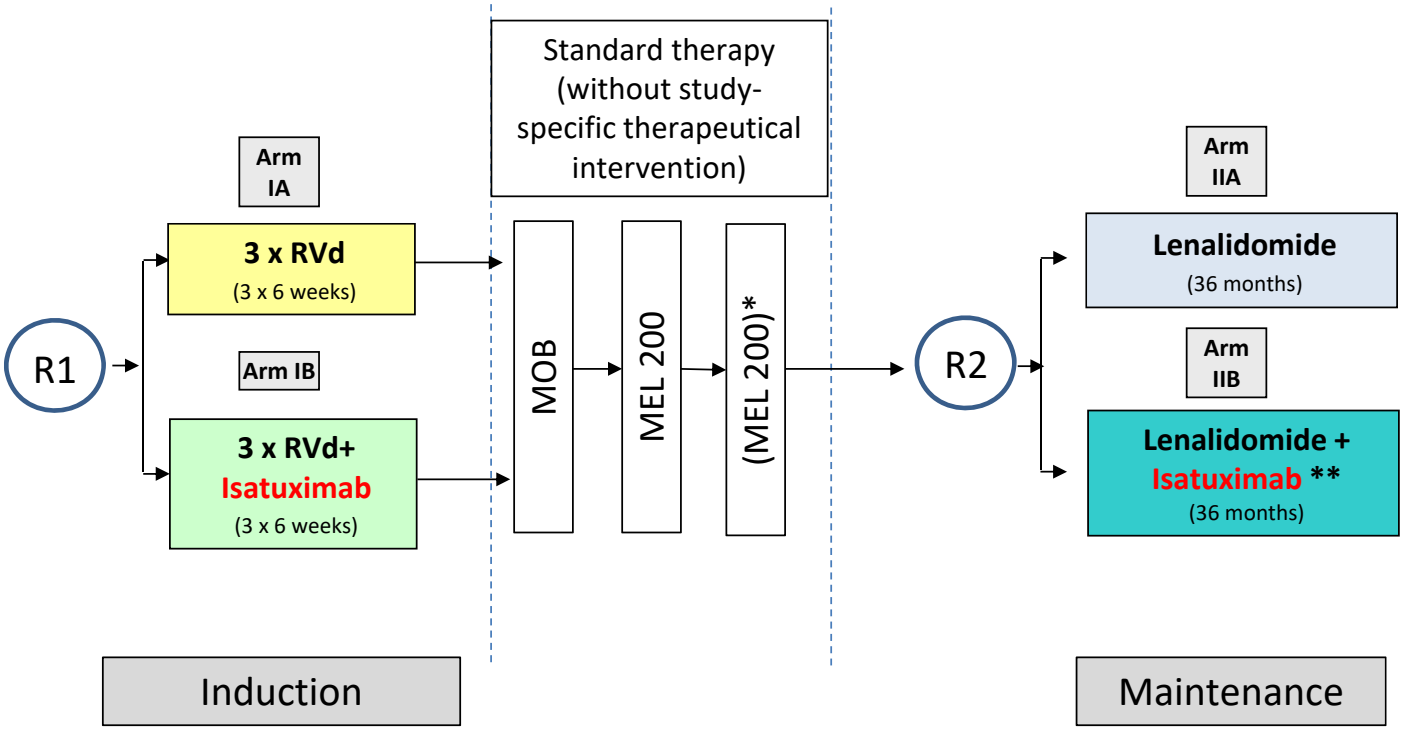


*2nd Mel200+ASCT if detectable M protein and/or > 5% clonal plasma cells

GMMG-HD7 Trial

(Modified trial design 19-Jan-2018)

Leiter der klinischen Prüfung: Hartmut Goldschmidt, Heidelberg
Co-PI: Katja Weisel, Hamburg



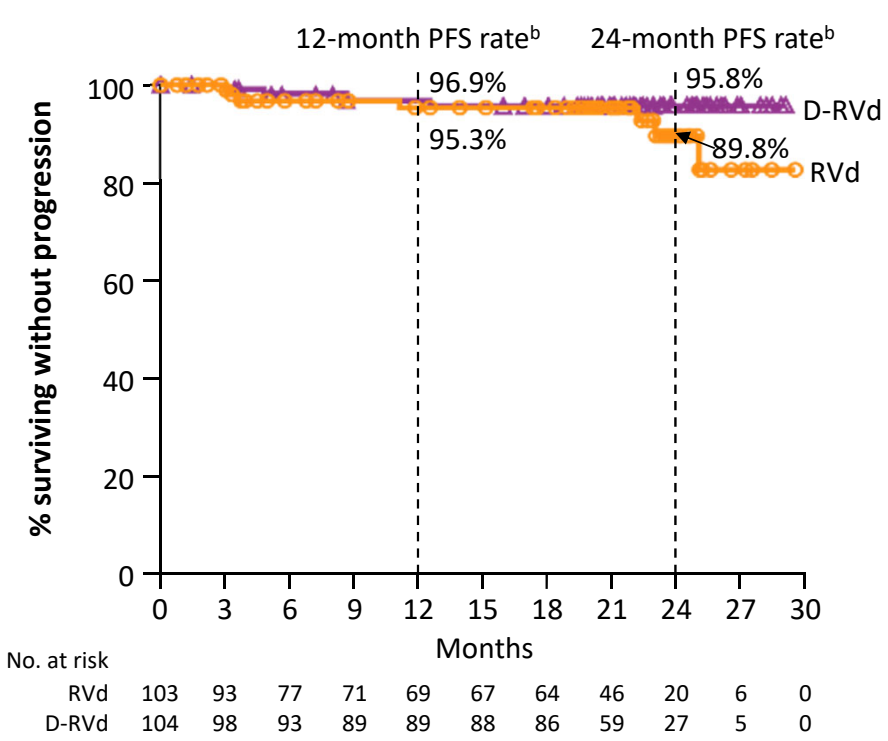
R1 = 1st randomization (at study inclusion); R2 = 2nd randomization (prior to maintenance)

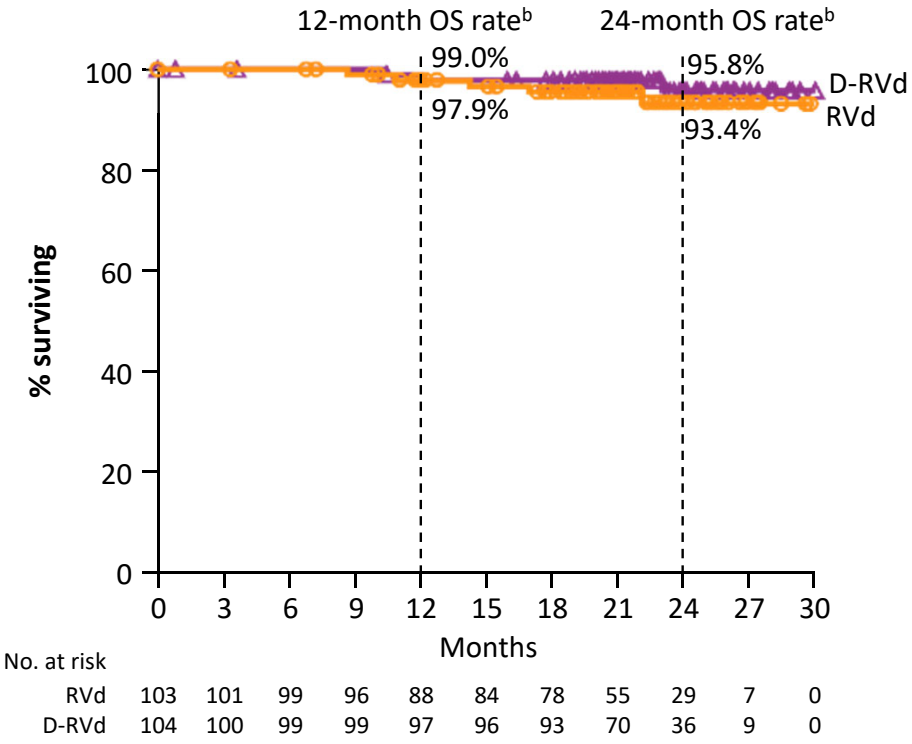
* decision for 2nd high dose therapy response-adapted (in case no CR)

*** Lenalidomide/Isatuximab for 36 months (thereafter, continuation of lenalidomide recommended until PD)*

Quadruple Induktion / Konsolidierung
D-RVd Results in Durable Estimated PFS and OS (>95%) at 2 Years[a]

- Median follow-up = 22.1 months

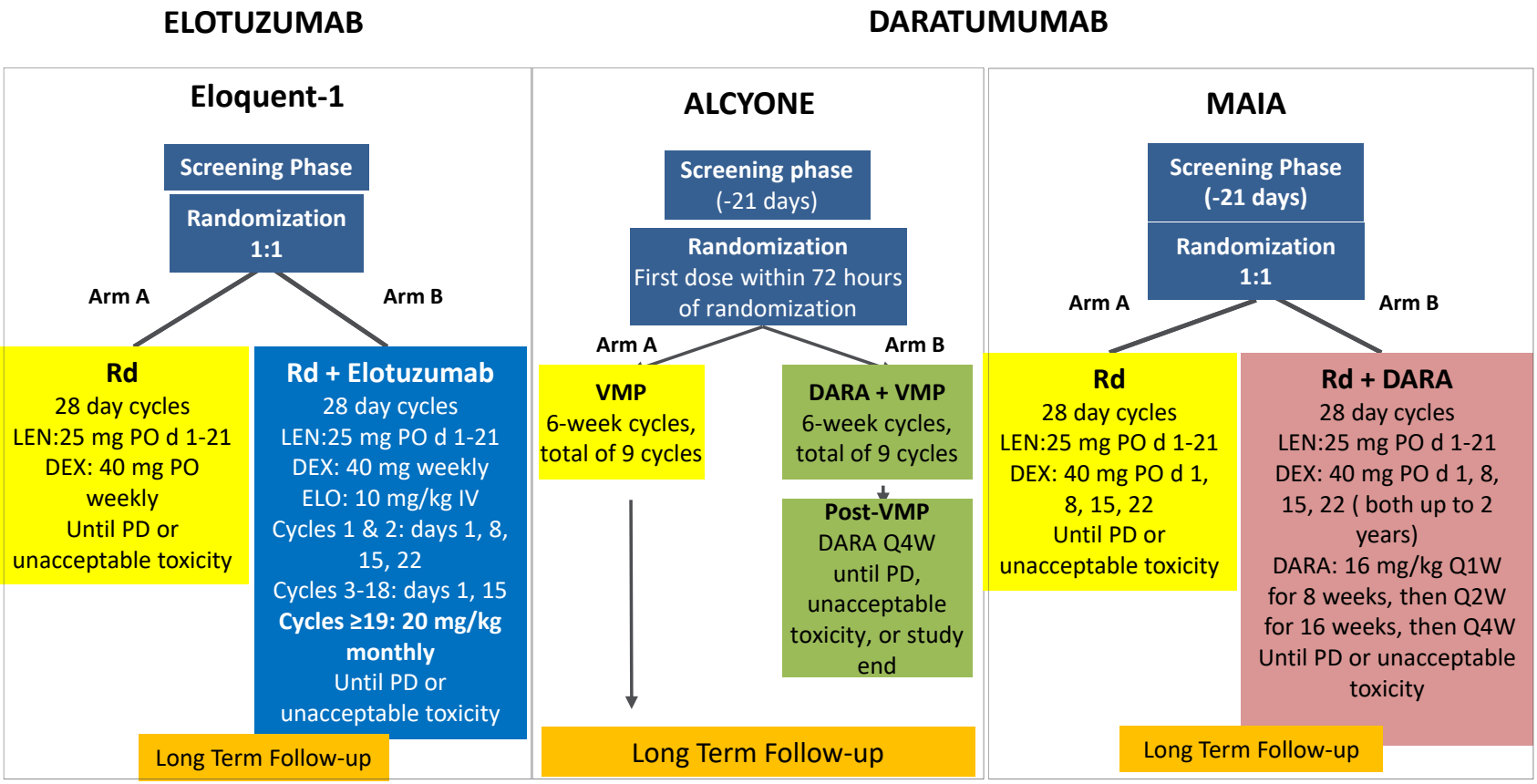




- **Median PFS and OS not reached for D-RVd and RVd**
- **Overall safety profile of D-RVd is consistent with previous reports of daratumumab plus SOC**
- **Stem cell mobilization was feasible and hematopoietic reconstitution was not impacted with D-RVd**

Voorhees et al., ASH 2019; abstract 691

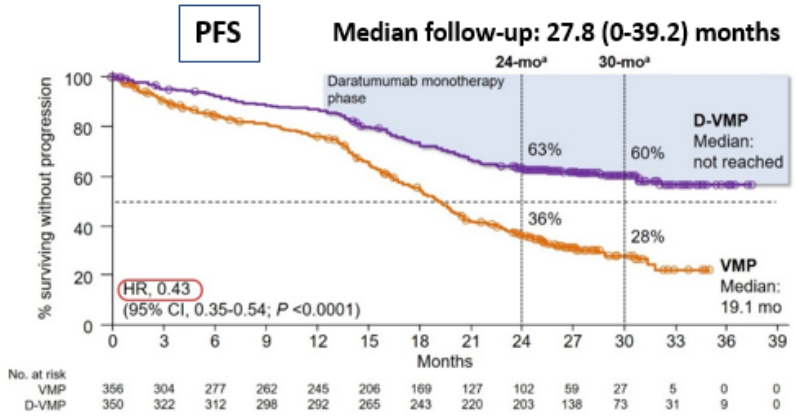
Behandlung der nicht-transplantationsfähigen Patienten (Alter > 70-75 Jahre, deutliche Co-Morbidität)



www.clinicaltrials.gov

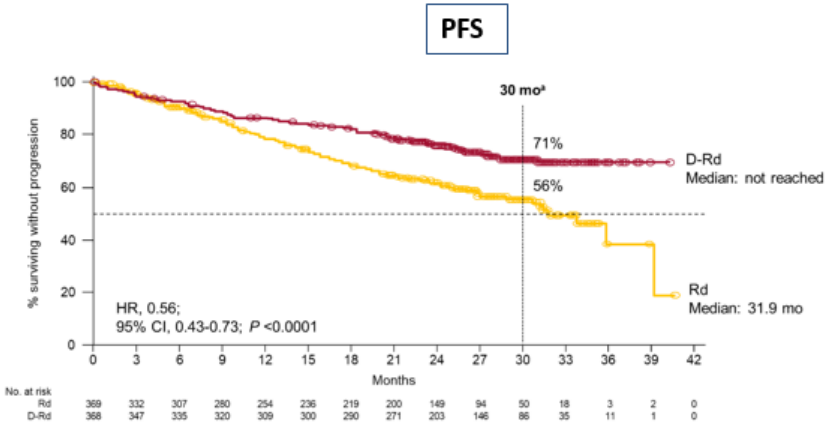
Was können wir mit den neuen Therapien (mit MoAK) bei älteren Myelompatienten erreichen?

phase III ALCYONE study



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

phase III MAIA study

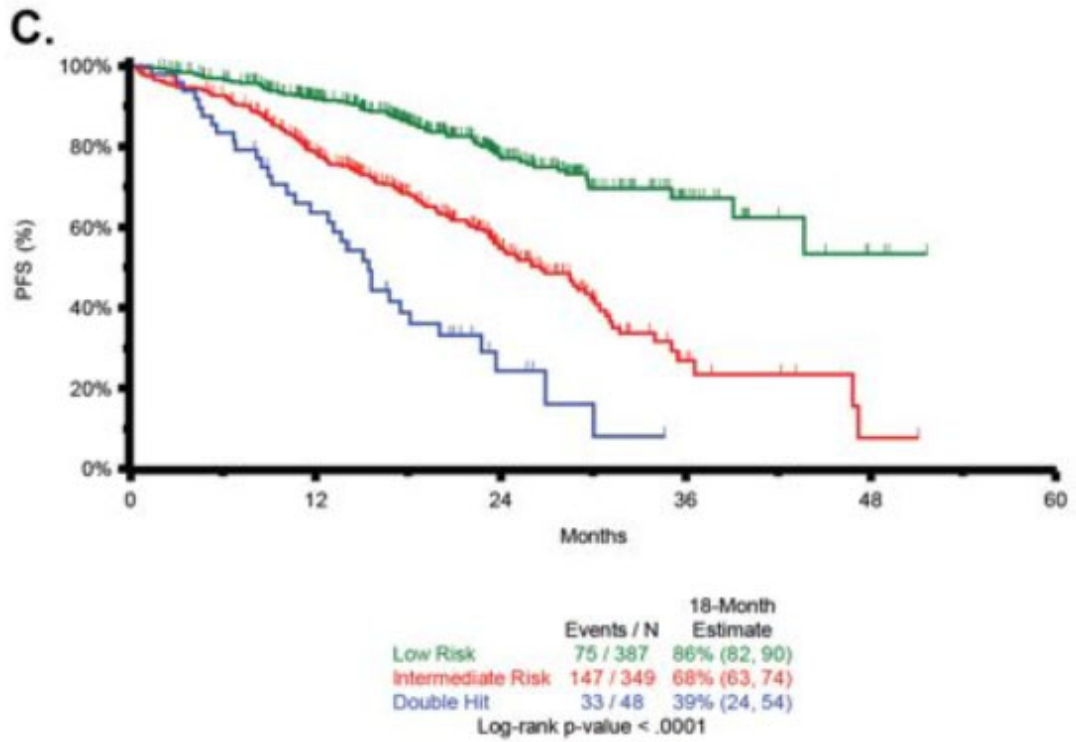


Facon T et al, N Engl J Med. 2019;380(22):2104-2115

- 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 !

➡ Bei älteren Myelompatienten ohne SZT zwar längere Remissionszeiten, aber keine Heilung!

Unmet medical need: Hochrisiko, v.a. Ultrahochrisiko-Patienten



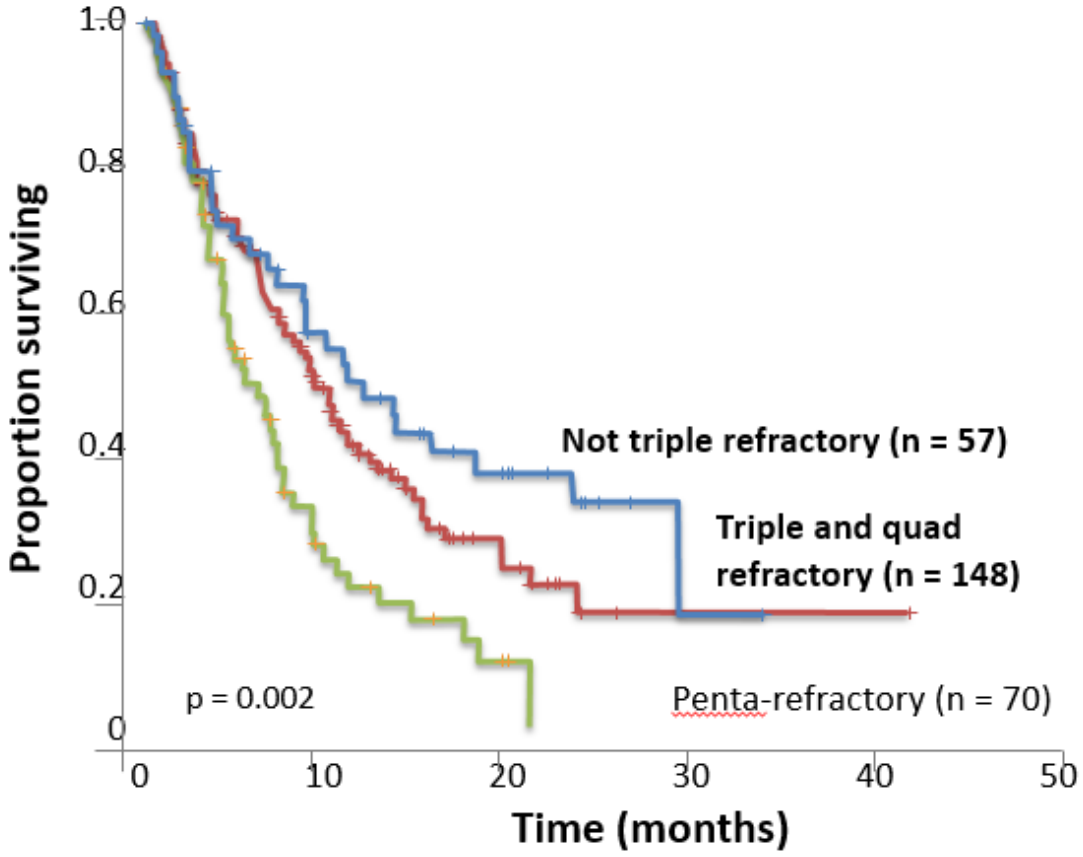
Walker BA et al, Leukemia. 2018 Jul 2

Characteristics: Bi-allelic inactivation of TP53 or ISS III + amplification of CKS1B
Median PFS = 15.4 months; OS = 20.7 months
→ Candidates for upfront therapy with novel cellular immunotherapy

Unmet Medical Need:
Patienten, refraktär auf PI/IMiD und anti-CD38 MoAK

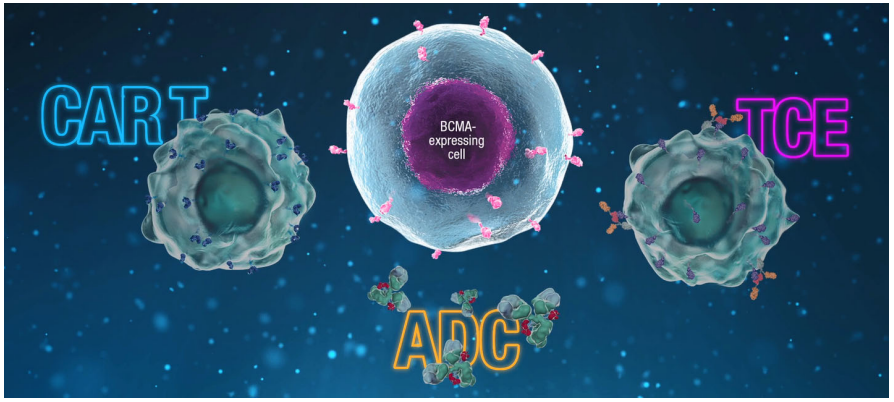
- 275 MM patients refractory to anti-CD38 mAbs
- mOS from refractoriness to CD38:
  - all patients: 8.6 months
  - "non-triple-refractory": 11.2 months
  - "triple- and quad-refractory": 9.2 months
  - "penta-refractory": 5.6 months

- 249 patients received further treatment:
  - mPFS: 3.4 months
  - mOS: 9.3 months

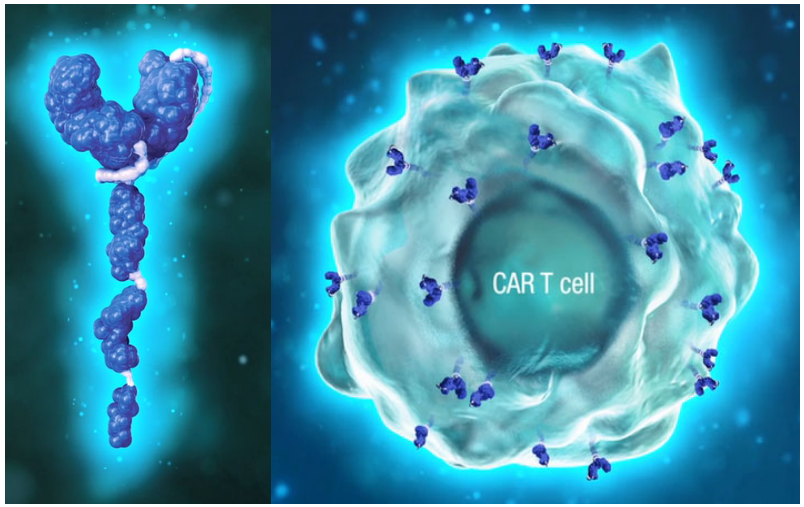


Gandhi UH, et al. Leukemia. 2019 Sep;33(9):2266-2275

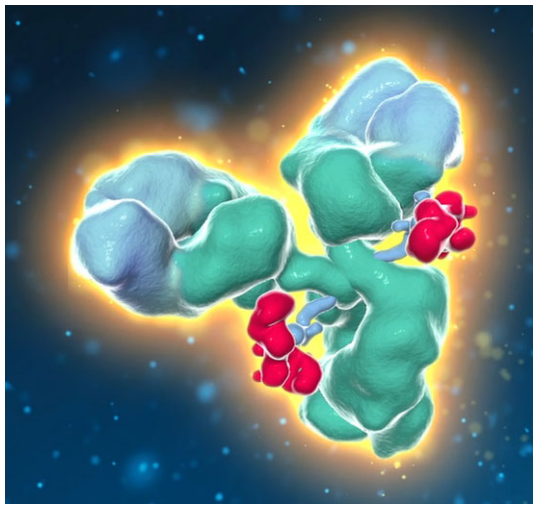
Zusätzlich zu den MoAK (anti-CD38: Daratumomab/anti-SLAMF7, Elotuzumab) jetzt BCMA-gerichtete Immuntherapeutika



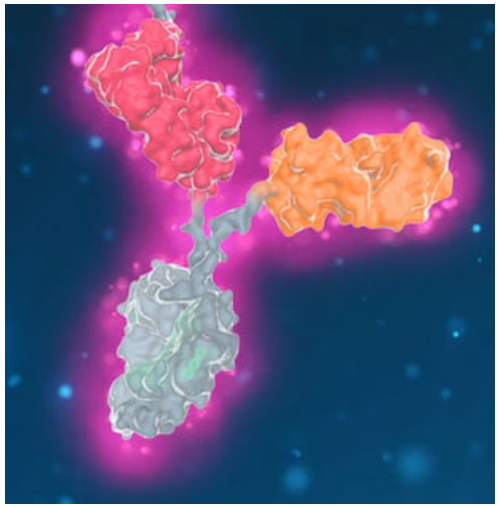
CAR T Cellular Therapies



Antibody-Drug Conjugates



T Cell Engagers



DREAMM-1: BCMA ADC Belantamab Mafodotin bei Patienten mit RRMM, Sicherheit und Wirksamkeit

Safety

Corneal events were the most frequently reported AE (69%)
Median duration was 35 days among the 16 patients with a resolution date

Most Common AEs, n (%)	N = 35
Corneal events	24 (69)
Blurred vision	18 (51)
Dry eye	13 (37)
Photophobia	10 (29)
Thrombocytopenia	22 (63)
Treatment-related SAEs	7 (20)
IRR	2 (6)

Previous therapies		Part 2 (n = 35)
> 5 lines of therapy, %		40
PIs, %	Received Refractory	100 97
IMiD compounds, %	Received Refractory	100 94
POM, n (%)	Received Refractory	63 63
DARA, %	Received Refractory	40 40
CFZ, %	Received Refractory	83 77

Efficacy

ORR = 60%
ORR, prior dara: 42.9%
ORR, IMiD + PI refractory: 56.3%
ORR, IMiD + PI ref, prior dara: 38.5%

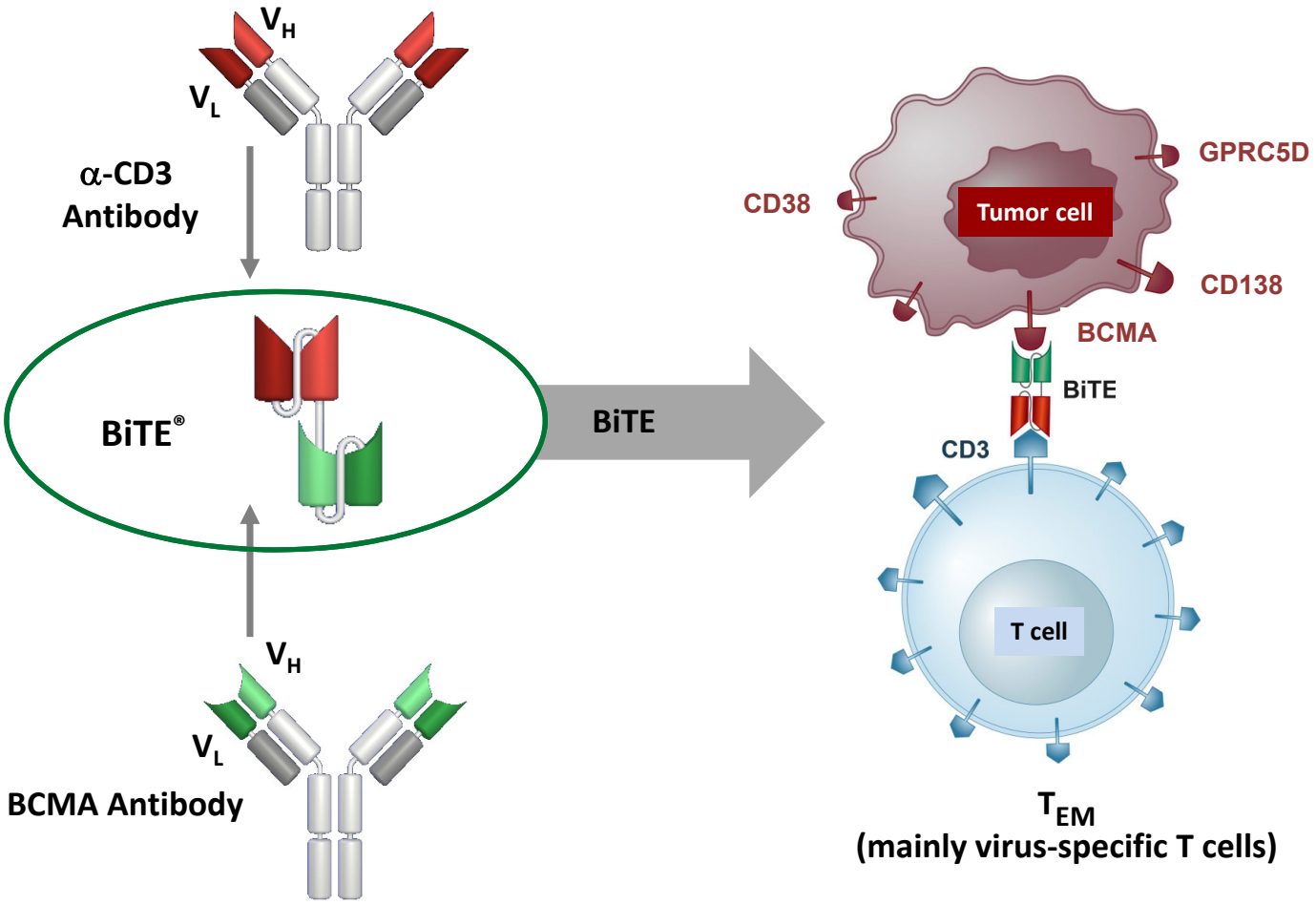
mPFS, ITT: 12 mo

- mPFS, prior dara 6.8 mo
- mPFS, IMiD + PI refractory: 7.9 mo

Trudel et al. Blood Cancer J. 2019;9:37.
Popat et al. EHA 2019: Abstract PS1372.

Bispezifische Antikörper: BiTE Format

Ziel: Erhöhung der Frequenz an Tumor-reaktiven T-Zellen



→ Approval by (FDA 2017, EC 2018) for r/r PB-ALL, MRD + PB-ALL (FDA 2018, EC 2019)

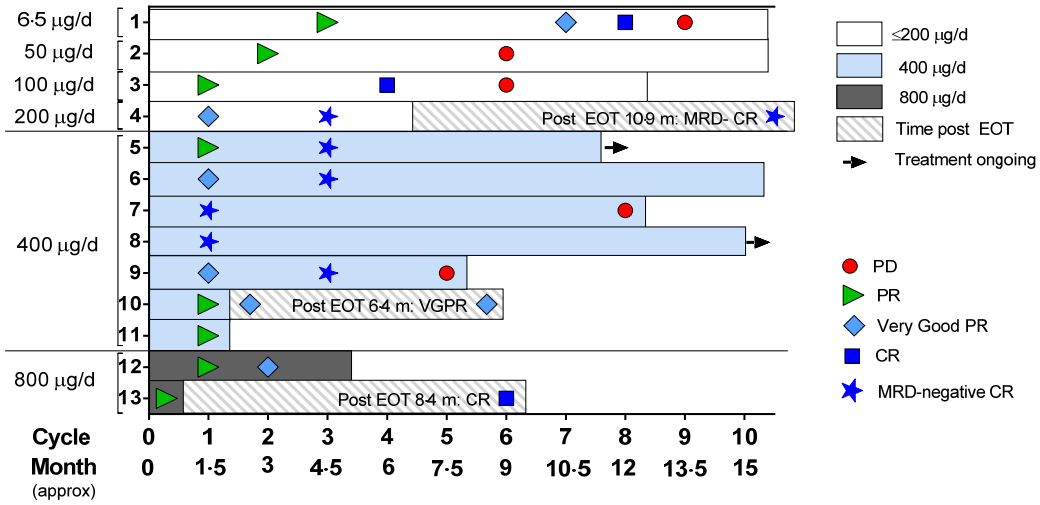
AMG 420, eine (BCMA) BiTE® Studie für r/r MM

(Median 3-4 Vortherapien)

Efficacy

- Responses
  - **At MTD 400 µg/d: 70% response rate**
  - **5 MRD-negative sCRs, 1 VGPR, and 1 PR**
- Duration of response: 5.6-10.4 months
- 4 patients ongoing on treatment
- **Several responses ongoing for > 1 year**

Responding patients



		N=42	# Gr 1	# Gr 2	# Gr 3	# Gr 4	# Gr 5
CRS	All treatment-related, max grade	16 (38%)	13	2	1	-	-
SAEs in ≥2 patients	Infections	13 (31%)	-	3	8	-	2*
	Peripheral polyneuropathy	2 (5%)	-	-	2	-	-
Treatment-related SAEs	Peripheral polyneuropathy	2 (5%)	-	-	2	-	-
	Edema	1 (2%)	-	-	1	-	-

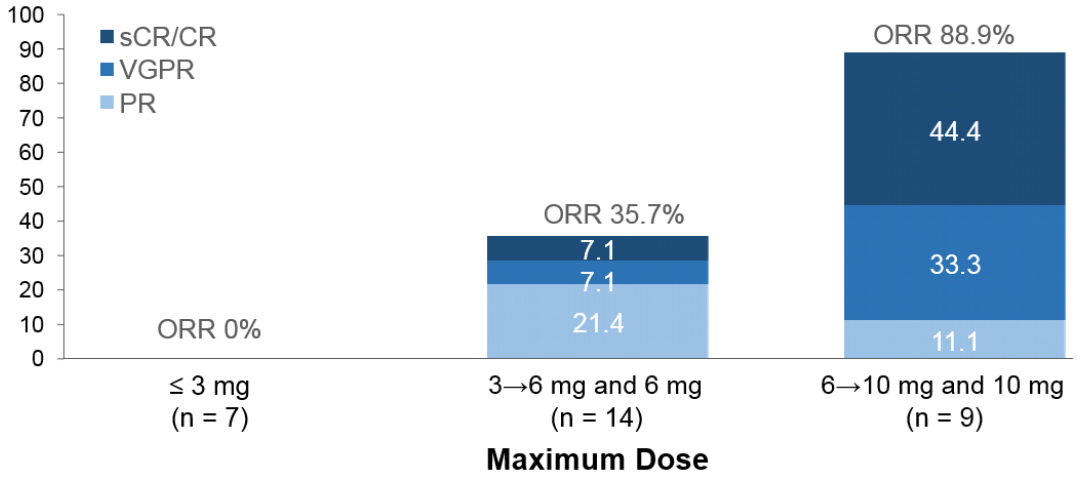
Topp MS, …… Einsele H, J Clin Oncol, 2020

* One patient died of aspergillosis / flu and one of fulminant hepatitis related to adenovirus infection, neither treatment-related.

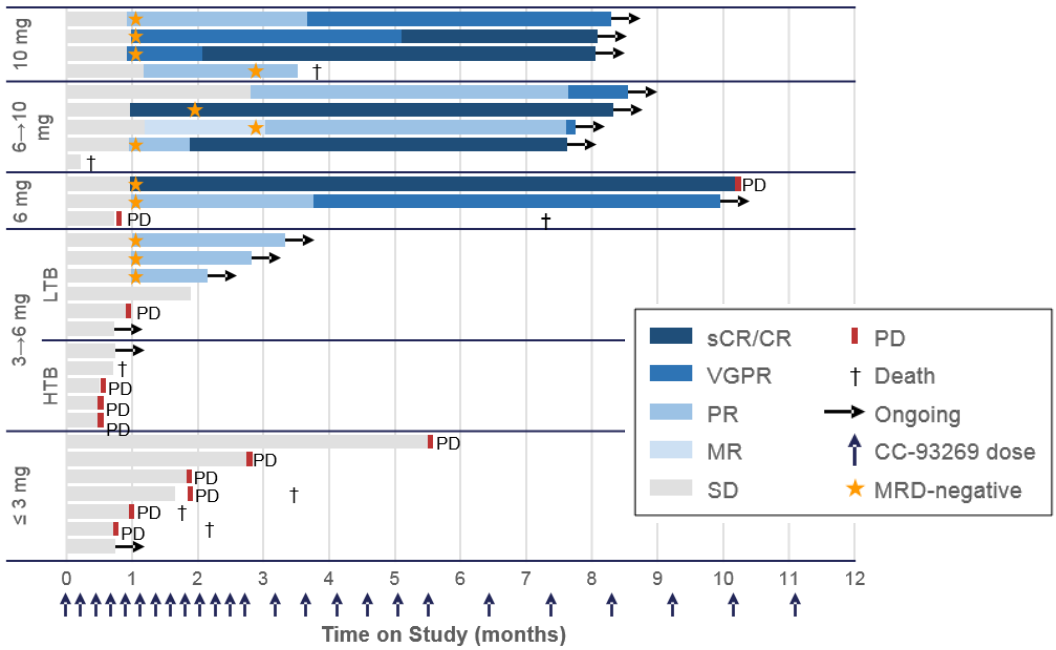
BCMA 2+1 T cell engager CC-93269: Efficacy

- Median age 64 years; median (range) 5 (3−13) prior regimens

Best overall response



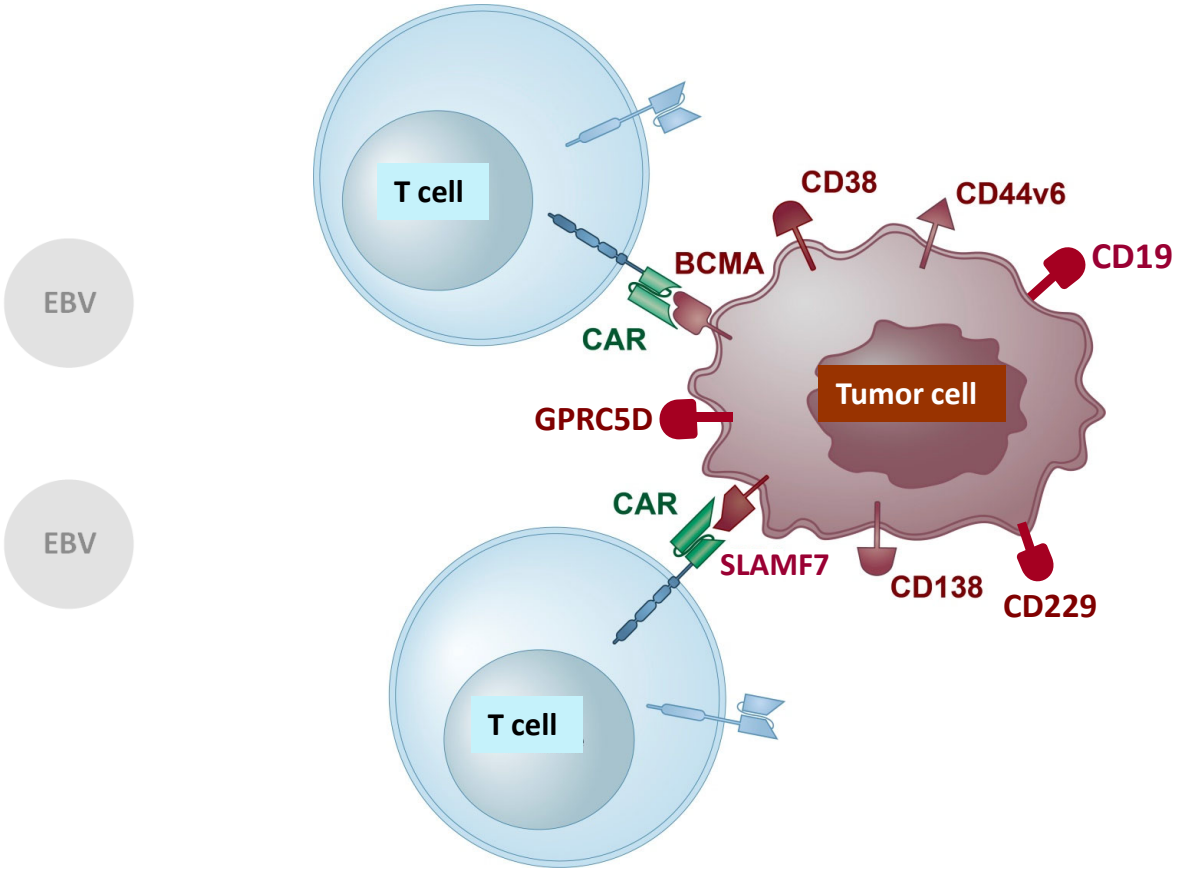
Response over time



- In all patients (N=30) ORR: 43.3%
- 5/30 (16.7%) patients achieved an MRD –ve (10^{-5}) sCR/CR

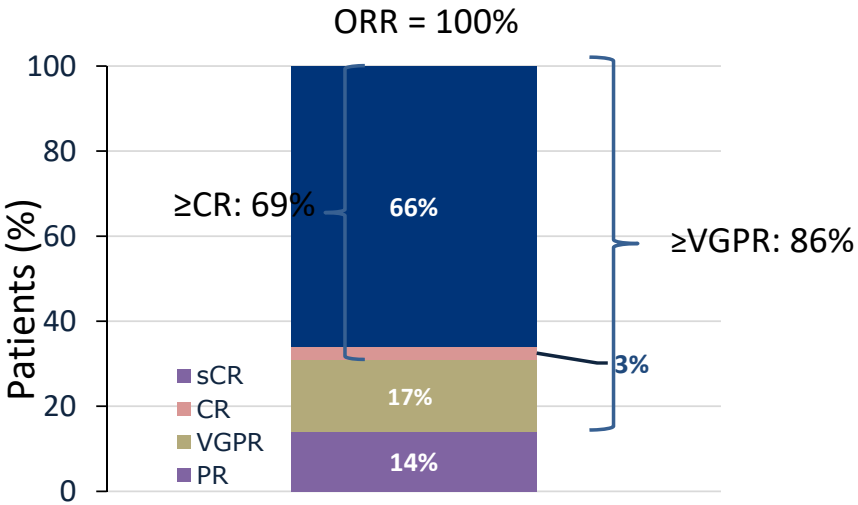
Costa et al., ASH 2019; abstract 143

Next CAR T Cell Therapy to be approved?!
CAR T Cell Therapy in Multiple Myeloma



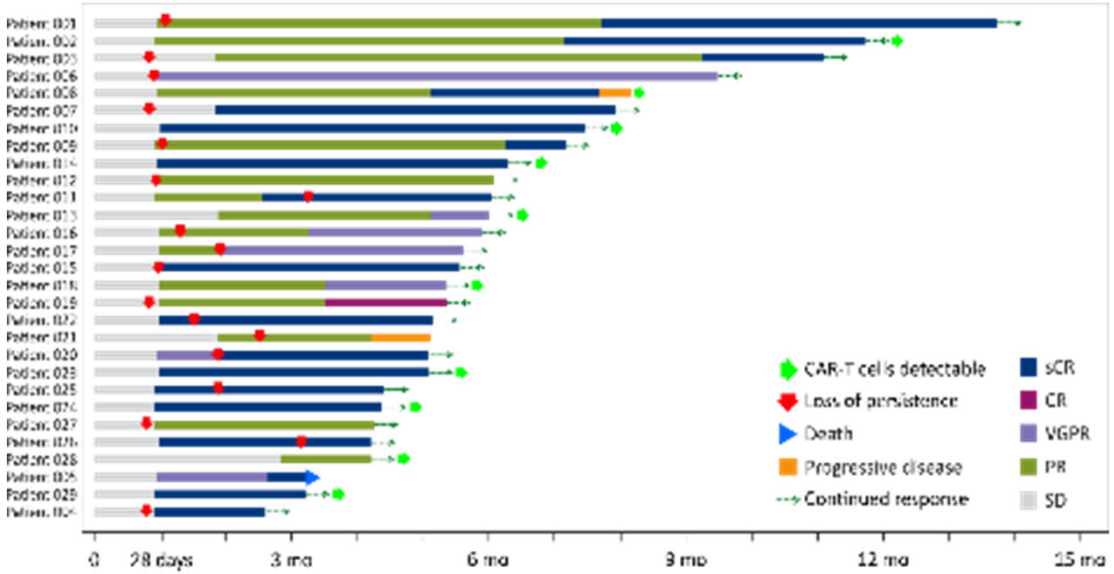
Translational Analysis from CARTITUDE-1, an Ongoing Phase 1b/2 Study of JNJ-4528 BCMA-targeted CAR-T Cell Therapy in Relapsed and/or Refractory Multiple Myeloma

Overall Response (n=29)*



Post-infusion day 28 BM Samples	
MRD-negativity, n	n=15
10^{-5}	10
10^{-4}	2
Unidentified clones	3

Durable Responses After Loss of JNJ-4528 Persistence in the Periphery



27/29 patients are progression-free at median 6-mo follow-up

Madduri D, et al. ASH 2019. Oral Presentation.

Phase 2 KarMMa study: Idecabtagene vicleucel (ide-cel; bb2121)

- Open-label, single arm study: N=140
- ≥ 3 prior therapies (including an IMiD, a PI and an anti-CD38 antibody); refractory to last regimen
- 94% of patients refractory to anti-CD38 antibody; 84% triple-refractory
- Median follow-up: 11.3 months

Efficacy

	Ide-cel Treated Population			
	150 x 10^6 CAR+ T cells (N=4)	**300 x 10^6 CAR+ T cells (N=70)**	**450 x 10^6 CAR+ T cells (N=54)**	**150–450 x 10^6 CAR+ T cells (N=128)**
ORR, n (%)	2 (50.0)	48 (68.6)	44 (81.5)	94 (73.4)
CR/sCR, n (%)	1 (25.0)	20 (28.6)	19 (35.2)	40 (31.3)
Median DoR, months	---	9.9	11.3	10.6
Median PFS, months	---	5.8	11.3	8.6

Median DOR and median PFS are not reported for the 150 x 10^6 CAR+ T cells dose group due to the small number of evaluable patients

- Grade ≥ 3 CRS: 5.5%
- Grade ≥ 3 investigator identified neurotoxicity events: 3.1%

Bristol-Myers Squibb and bluebird bio press release, Dec 6, 2019

Zusammenfassung

Erstlinientherapie:

- Bei Patienten < 70-75 Jahre:
  - weiterhin HD-Mel plus Auto-SZT Therapiestandard
  - Induktionstherapie und Konsolidierung mit Quadruple-Kombinationen (z.B. VRD + Dara) und Erhaltung mit Rev (+ Dara ?)

- Beim Patienten > 70-75 Jahre oder Co-Morbiditäten:
  - Dara-VMP oder Dara-Rd bis zum Progress

Neue Entwicklungen:

Zunehmend neue Immuntherapien beim fortgeschrittenen MM, aber auch in der 1. oder 2. Linie (CART, bispezifische Antikörper, Immunkonjugate)

COVID-19 and Multiple Myeloma
Major side effects/AEs of different agents

Agent	Selection of major side effects
Elotuzumab	Infusion reactions , infection ↑
Daratumumab	Infusion reactions, neutropenia, infection ↑
Isatuximab	Infusion reactions, neutropenia, infection ↑
Pomalidomide	↑ Infection, thromboembolism
Lenalidomide	↑ Infection, thromboembolism
Carfilzomib	Cardiac SAE
Bortezomib	PNP
Ixazomib	GI/nausea
Panobinostat	GI/nausea, fatigue
Cyclo/Melphalan/Benda	Hem tox, immunosuppression, infection ↑

Gengenbach,...Engelhardt. Leuk Lymphoma. 2018;59:2692-99
Delforge, Ludwig. Blood 2017;129:2359-67; Ludwig et al. Leukemia. 2018;32:1542-60
Engelhardt et al. Das Blaue Buch 7th edition 2019/2020

COVID-19 and Multiple Myeloma: Experience from the German Myeloma Trials

1. Recruiting at a slightly decrease rate (25 instead of 30 pts/month)
2. Induction therapy is performed without alterations (KRd-Elo/VRd-Isa)
3. SC collections – few centers use steady state mobilization
4. ASCT performed according to protocols (in a tandem SCT protocol few centers delay the second ASCT)
5. Lenalidomide maintenance is administered
6. COVID experience:
   - Few patients with COVID-19 infection during Len-maintenance (no ICU admission)
   - Few patients with COVID-19 6-10 weeks post SCT (no ICU admission)

Vielen Dank für Ihre Aufmerksamkeit!