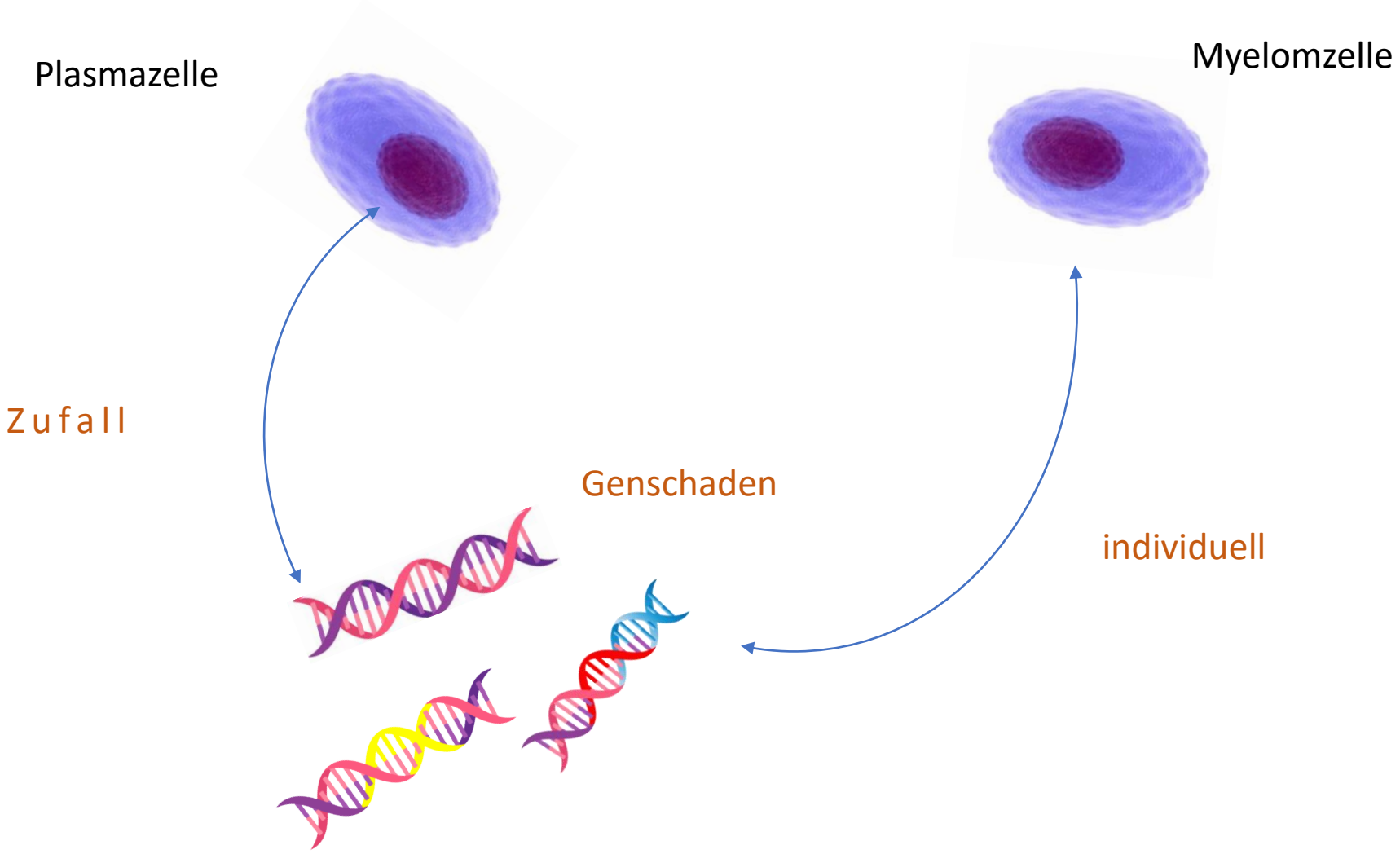
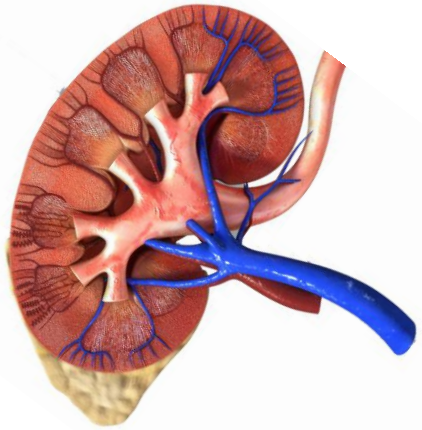
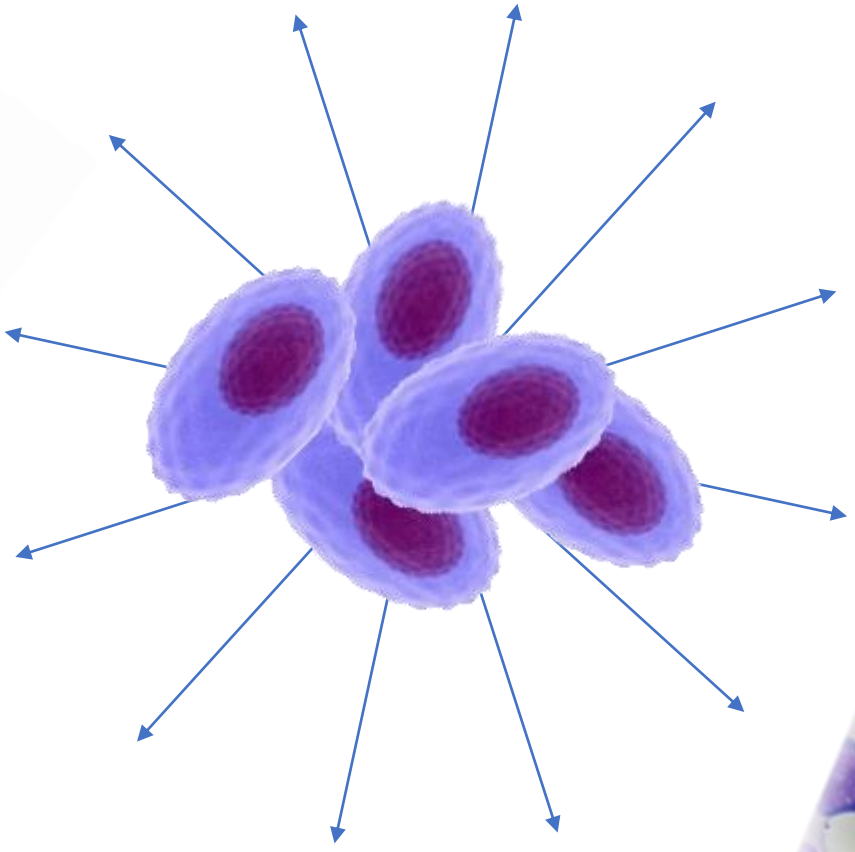
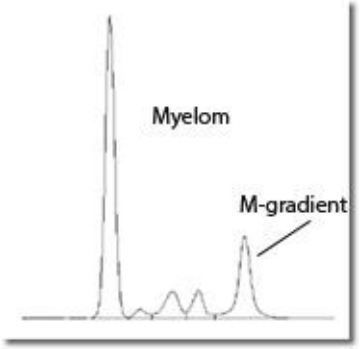
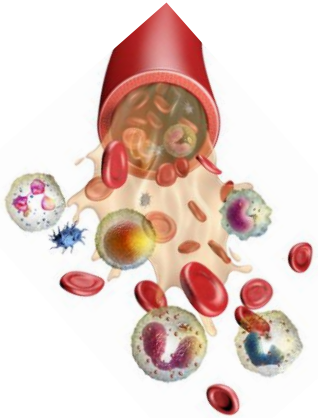
Myelom

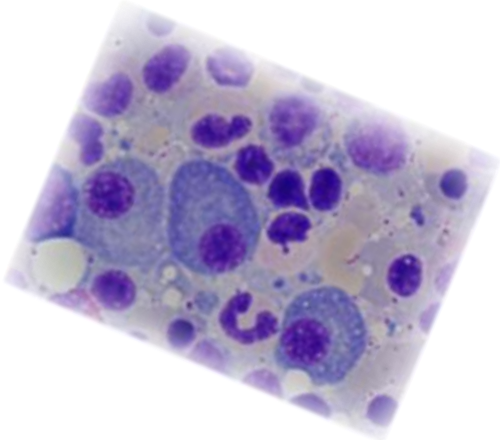

Plasmazelle
Myelomzelle
Zufall
Genschaden
individuell



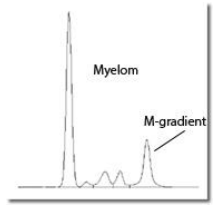


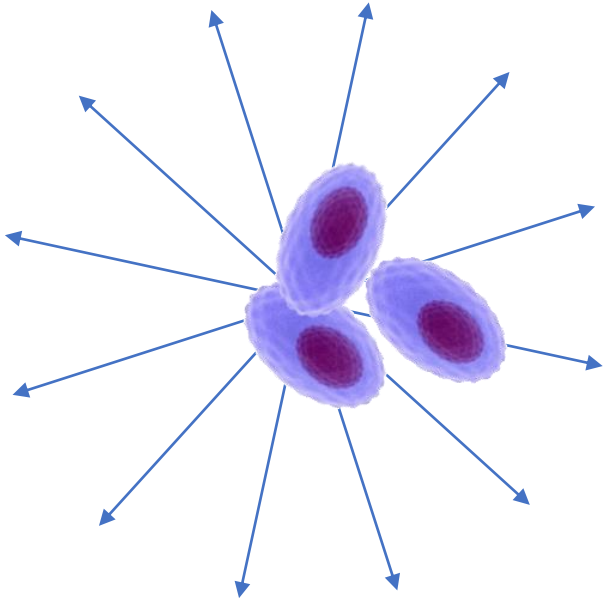

Myelom
M-gradient

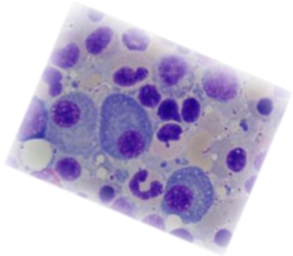




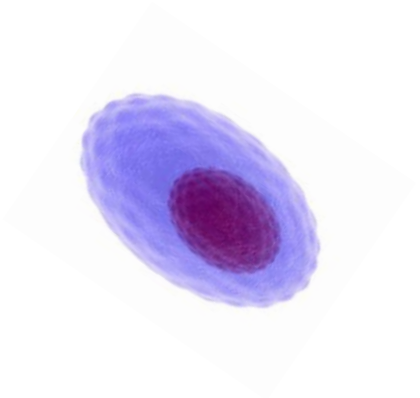
Therapie


Myelom
M-gradient





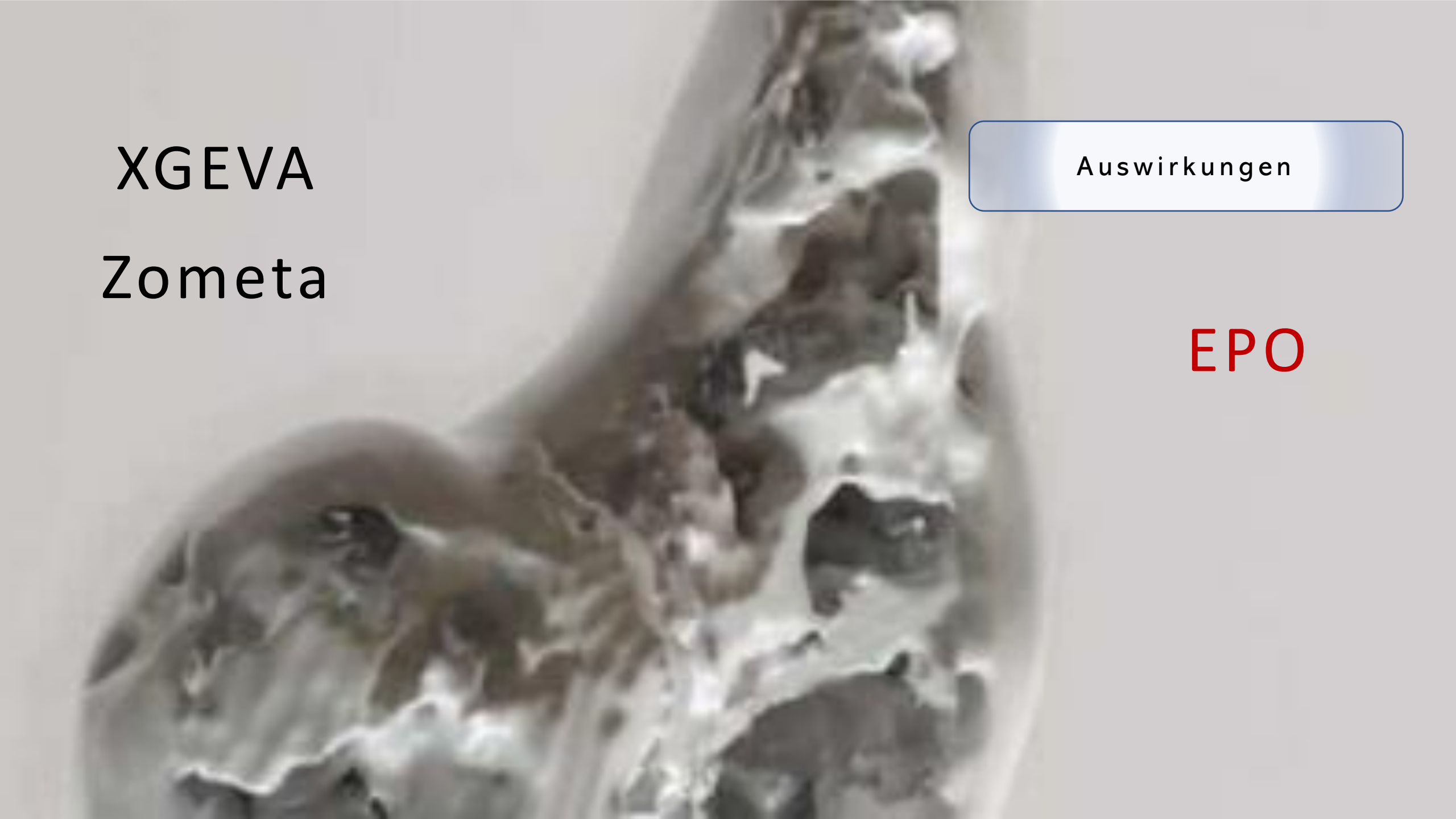
direkter Schaden



- Velcade, Ninlaro, Kyprolis
- Revlimid, Imnovid, Thalidomid
- Kortison
- Cyclophosphamid
- Bendamustin
- Melphalan
- autologe Transplantation

Immunabwehr

- Revlimid, Imnovid, Thalidomid
- Darzalex, Elotuzumab, Isatuximab
- CarT Zellen
- Allogene Transplantation



XGEVA

Zometa

Auswirkungen

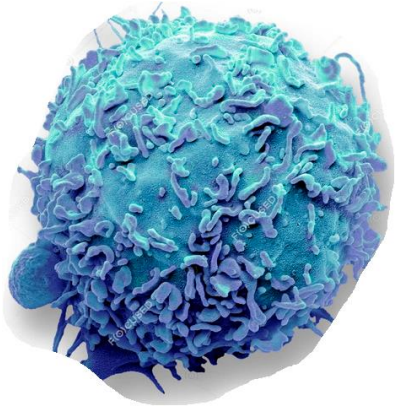
EPO

Neuigkeiten

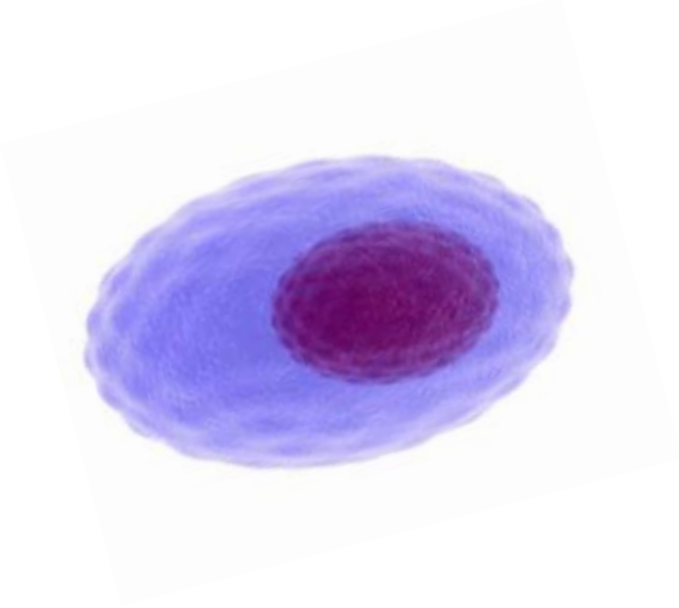
Immuntherapie

Voraussetzung ?

intake Immunzellen



Myelom

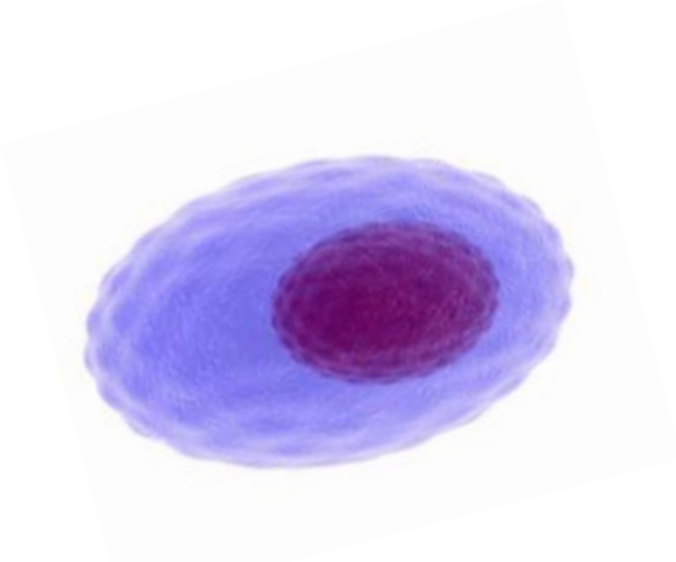


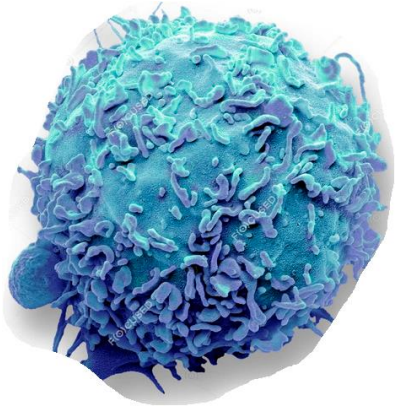
Einsatz in späten Therapielinien ?

Immunzellen

Myelom

Antikörper

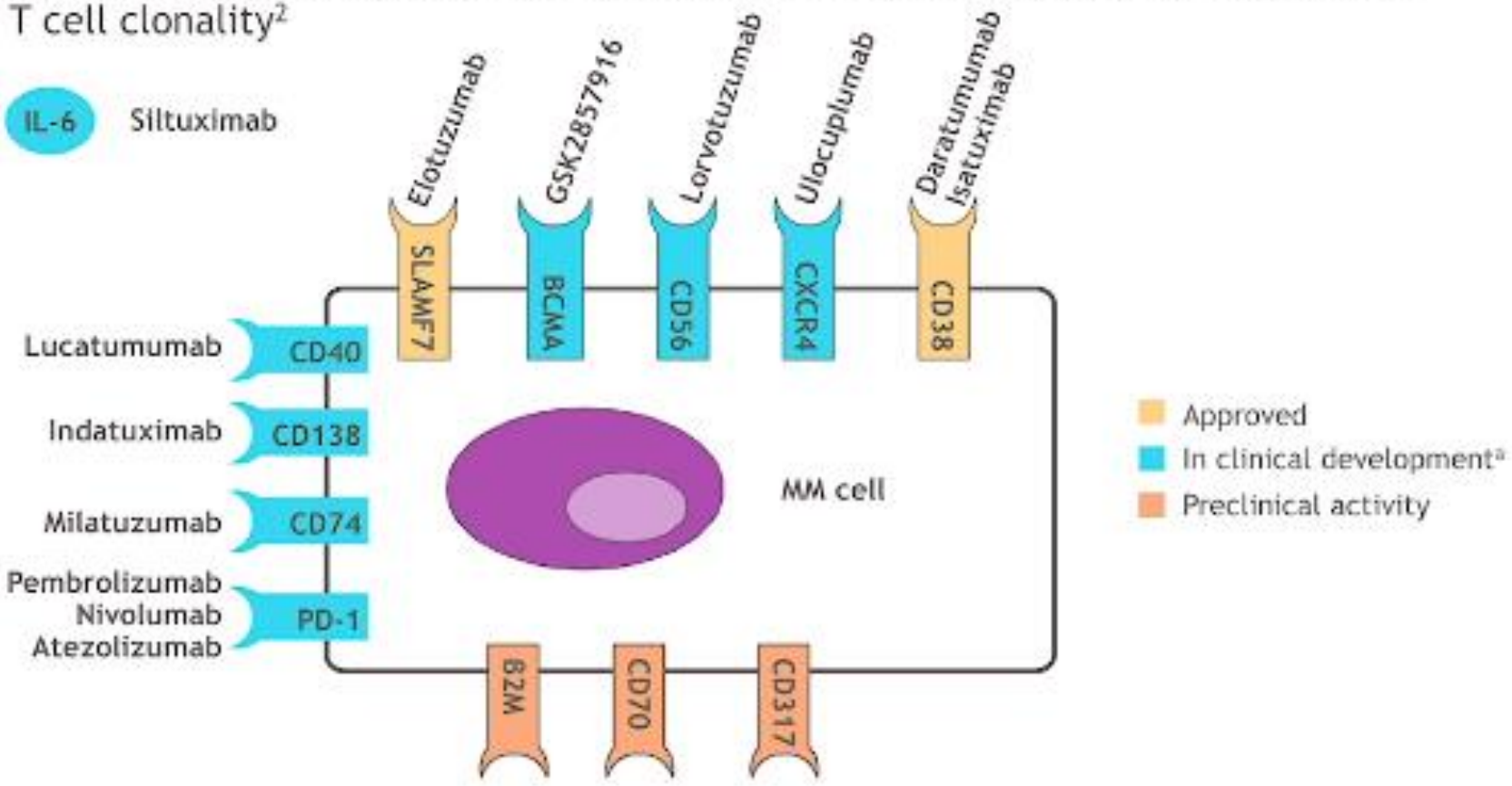




Verbindung – direkte Schädigung

Targets for monoclonal antibodies in MM

- Monoclonal antibodies work through ADCC, CDC or apoptosis / growth arrest[1]
  - Some deplete CD38-expressing immunosuppressive regulatory cells, which in turn promotes T cell expansion and activation and increased T cell clonality[2]



[a]Investigational only, not approved.
ADCC, antibody-dependent cell cytotoxicity; BCMA, B cell maturation agent; CDC, complement-dependent cytotoxicity.
1. Tai YT, Anderson KC. Bone Marrow Res. 2011;2011:924058. 2. Krejcik J, et al. Blood. 2016;128:384-94. Figure adapted from Lonial S, et al. Leukemia. 2016;30:526-35.

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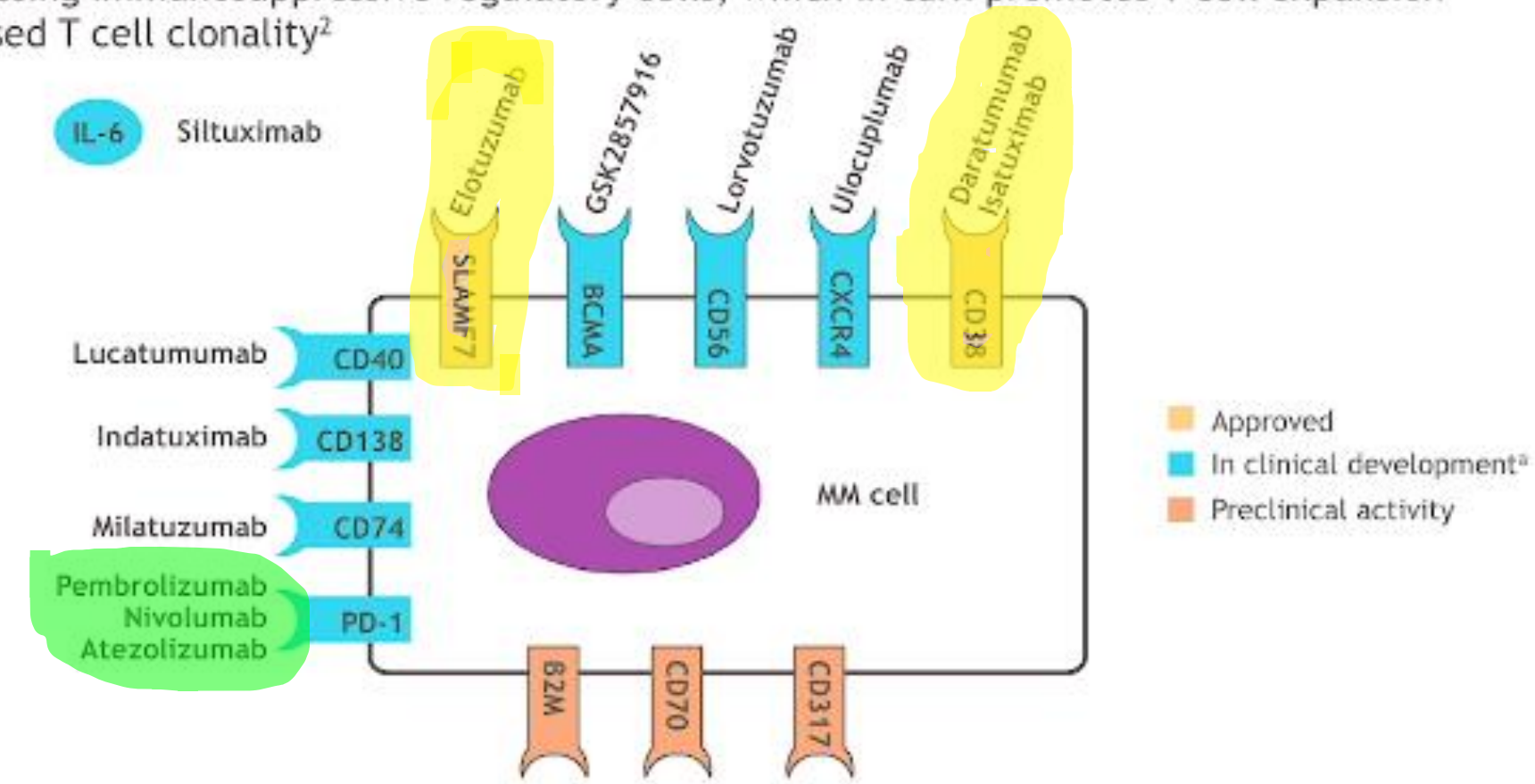

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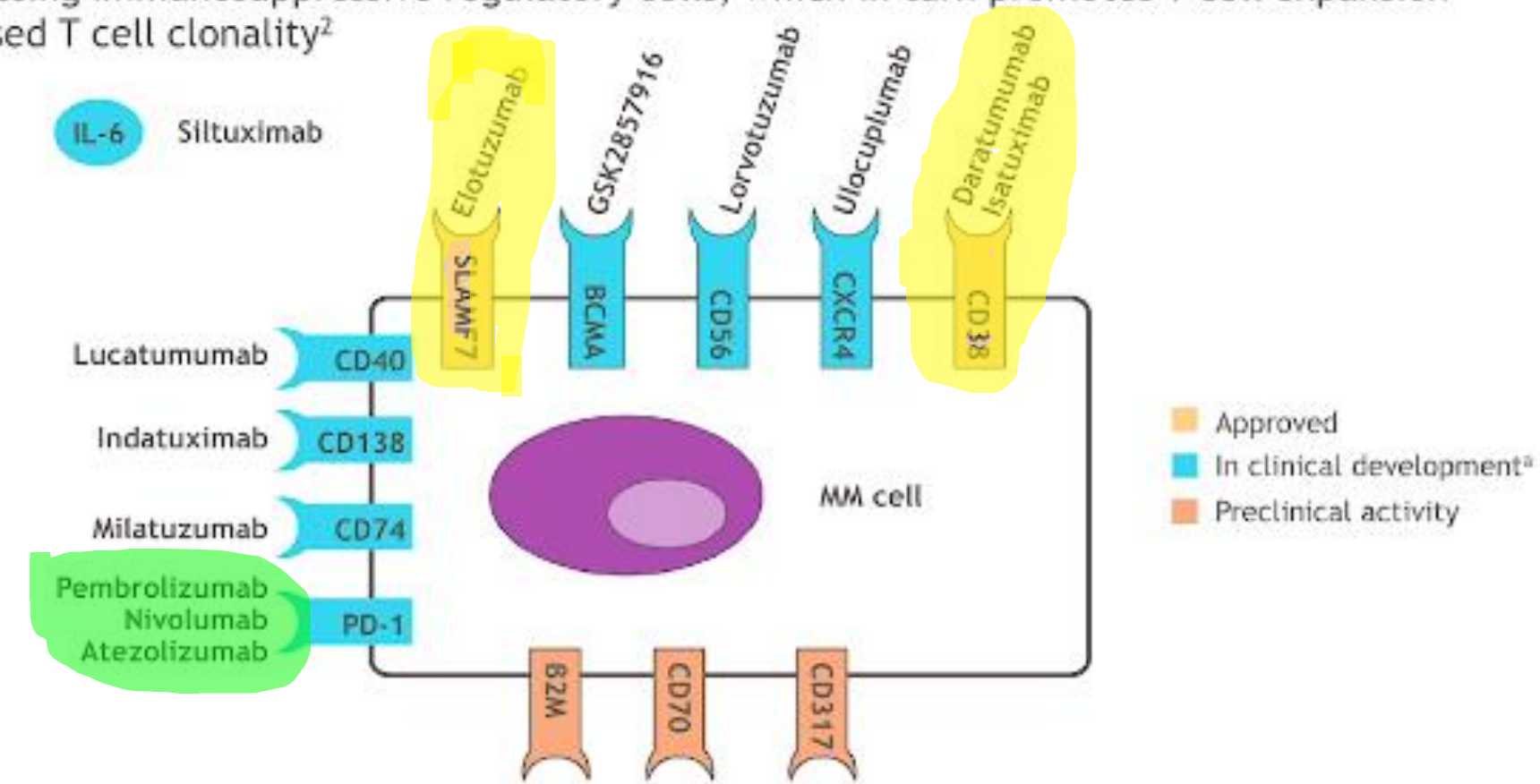
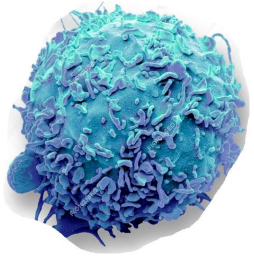


enthemmen die Wirkung



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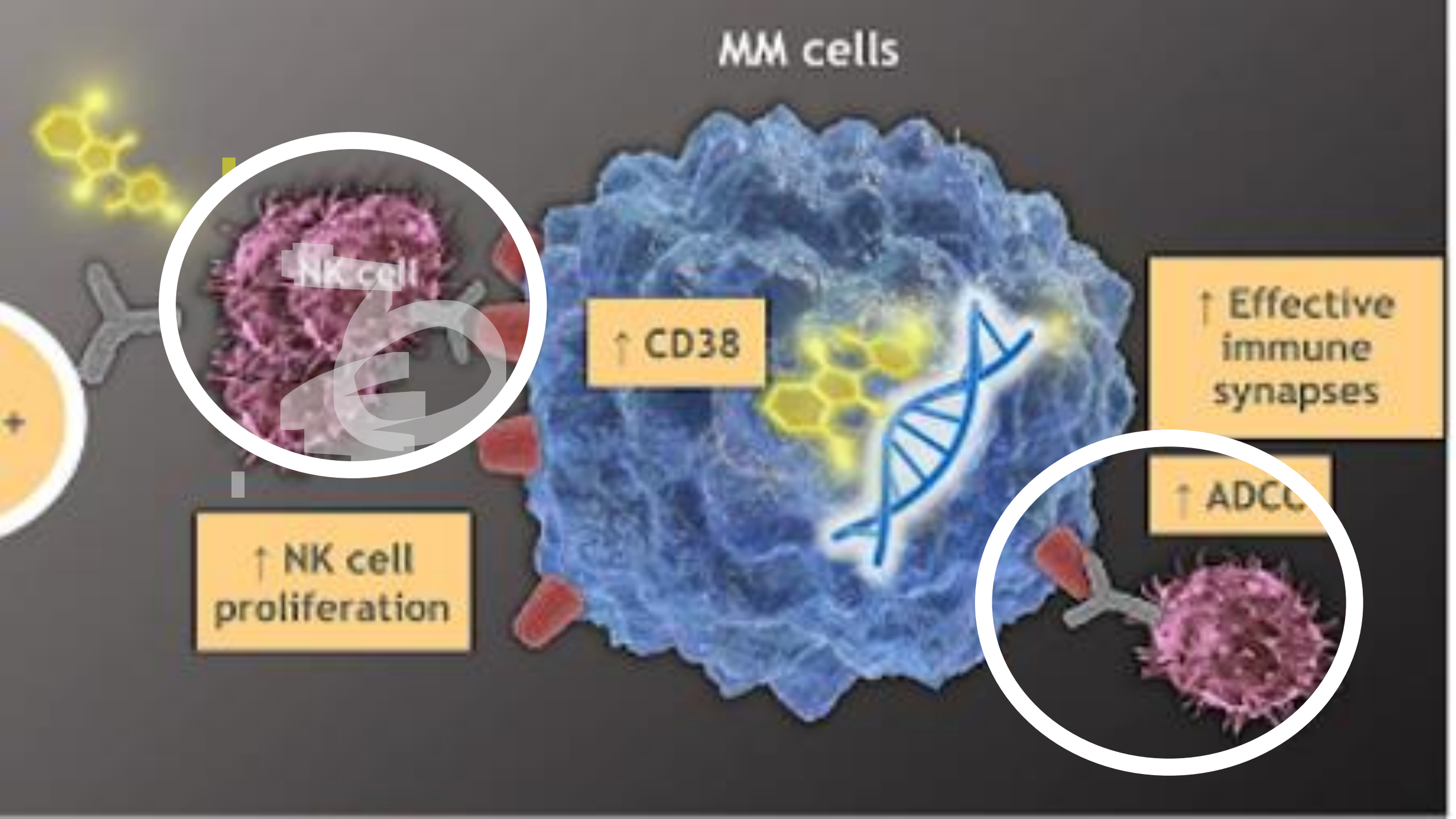
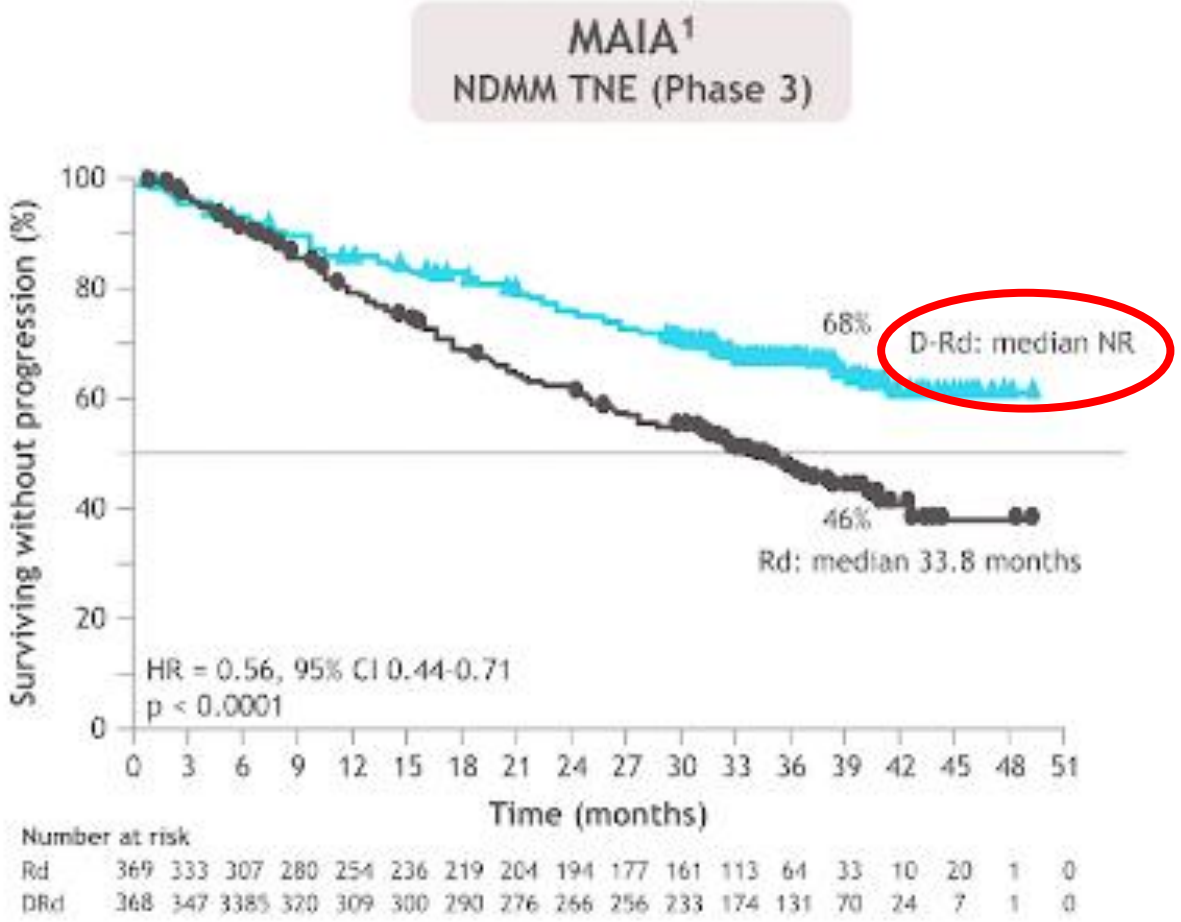
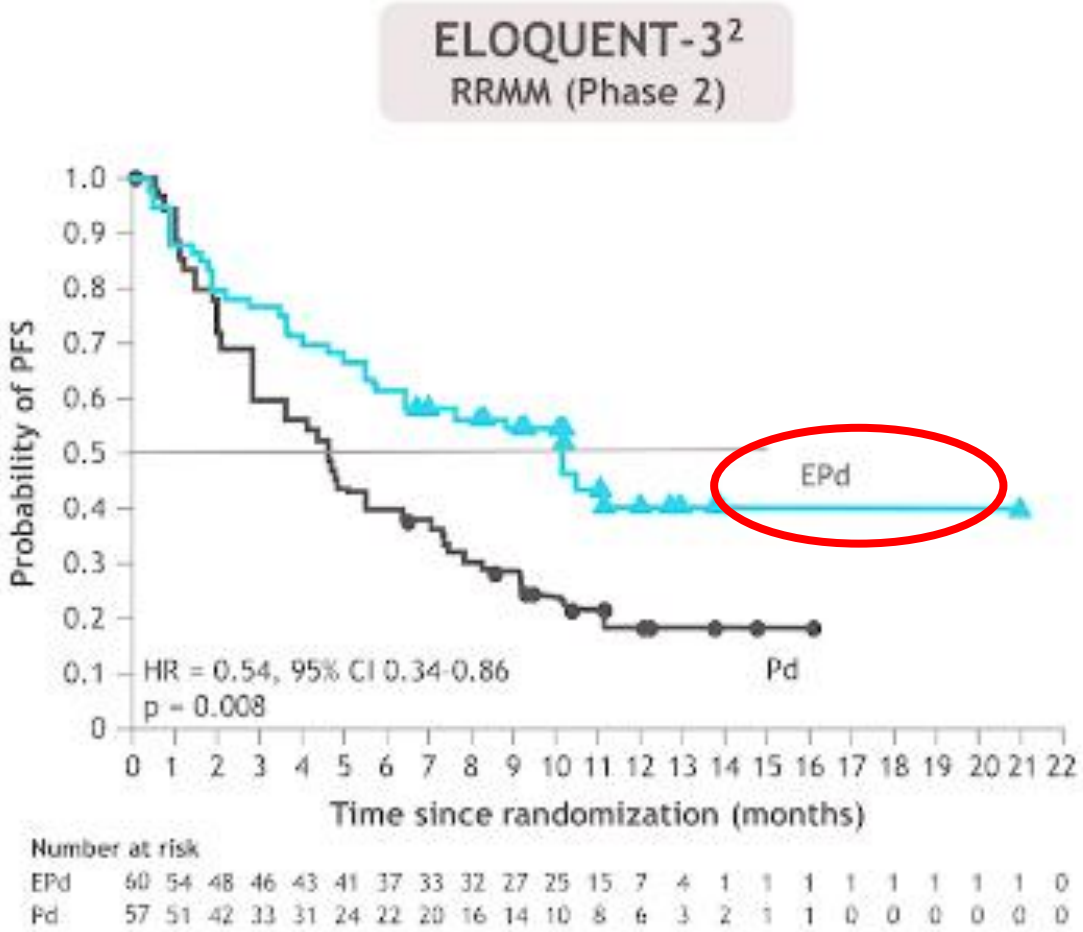

MM cells
NK cell
↑ CD38
↑ Effective immune synapses
↑ ADCC
↑ NK cell proliferation

Kombination von Revlimid, Imnovid, Thalidomid mit Antikörper – steigert die Immuntherapie - Wirkung

Combination therapies improve clinical outcomes





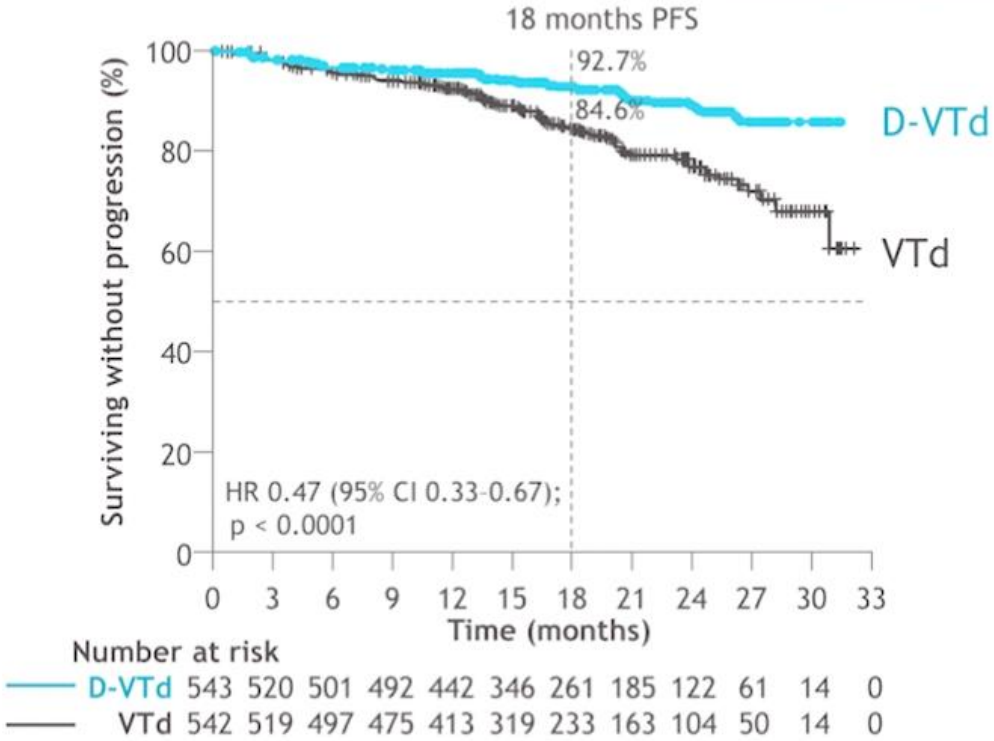
Direct comparison between trials is not intended and should not be inferred.

CI, confidence interval; D-Rd, daratumumab Rd; EPd, elotuzumab; HR, hazard ratio; NDMM, newly diagnosed multiple myeloma; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; RRMM, relapsed/refractory multiple myeloma.

1. Sahin N, et al. Blood. 2019;134(Suppl 1):1875. 2. Dimopoulos MA, et al. NEJM 2018;379:1811-22.

CASSIOPEIA: PFS and response assessment after consolidation

Median follow-up: 18.8 months



Response	D-VTd	VTd	OR (95% CI)	p value
sCR, %	29	20	1.60 (1.21-2.12)	0.0010
≥ CR, %	39	26	1.82 (1.40-2.36)	< 0.0001
≥ VGPR, %	83	78	1.41 (1.04-1.92)	0.0239
MRD negative (10^{-5}), %	64	44	2.27 (1.78-2.90)	< 0.0001
≥ CR + MRD negative (10^{-5}), %	34	20	2.06 (1.56-2.72)	< 0.0001

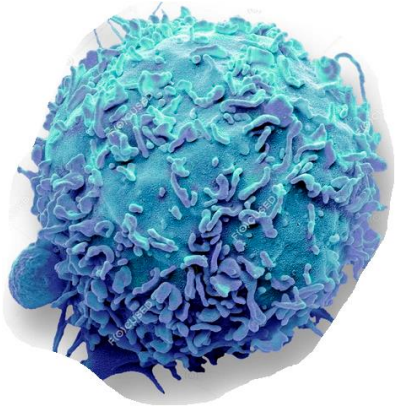
Grade 3 or 4 AEs of interest with D-VTd:

- Neutropenia (28%), thrombocytopenia (11%), lymphopenia (17%), peripheral neuropathy (9%), stomatitis (13%)

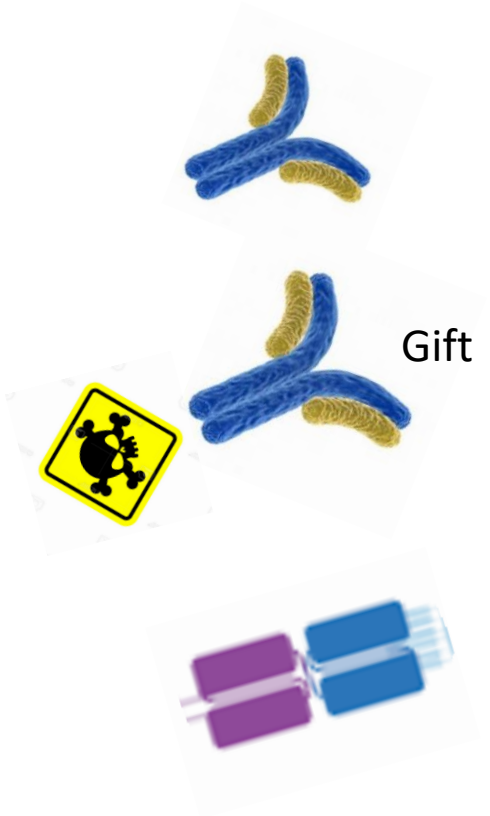
Other mAbs and ADCs for Myeloma: what's happening in 2019-2020

Target	Agent	Type (toxin)	Comments	Clinical Trials #*
CD38	Isatuximab	naked	phase 3 combo with pom/dex under FDA review	NCT02990338
CD38	TAK-079	naked	subcutaneous administration, phase 1 single-agent	NCT03439280
CD38	TAK-573	ADC (IFNα)	phase 1 single-agent	NCT03215030
CD38	TAK-169	ADC (shiga-like toxin A subunit)		preclinical
BCMA	SEA-BCMA	naked	phase 1 single agent	NCT03582033
BCMA	MEDI2228	ADC (PBD)	phase 1 single-agent	NCT03489525
BCMA	HDP-101	ADC (Amanitin)		pre-clinical
CD48	SGN48A	ADC (MMAE)	phase 1 single-agent	NCT03379584
CD46	FOR46	ADC (MMAF)	phase 1 single-agent	NCT03650491
CD56	IMGN901 (lorvotuzumab mertansine)	ADC (DM1)	2/37 (6%) ORR in phase 1	NCT00346255
CD74	STRO-001	ADC (SC236)	phase 1 single-agent	NCT03424603

Immunzellen



Antikörper



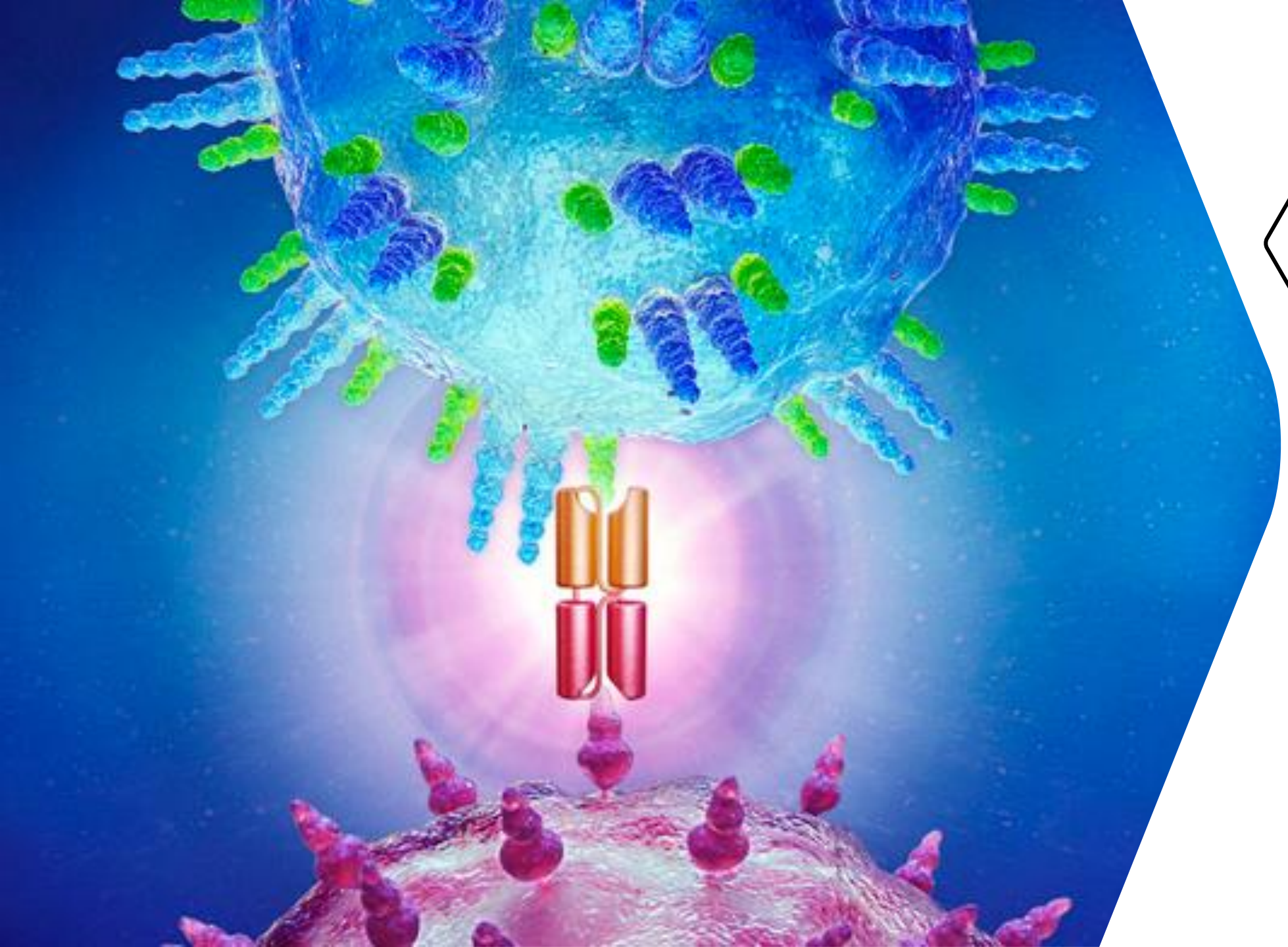
Gift

Brücke

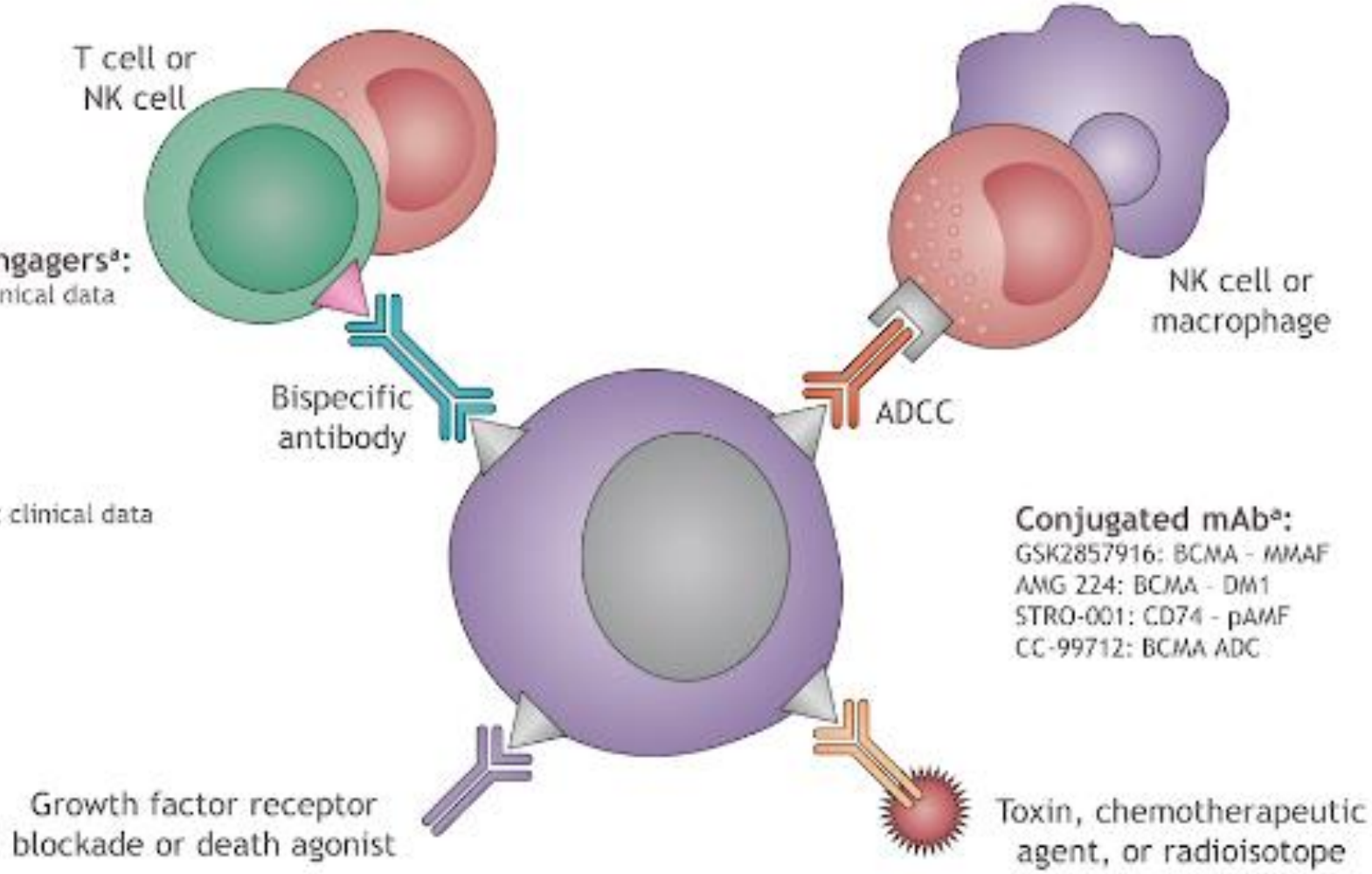
Myelom

Darzalex
Emplicity

Zulassung



Futures perspectives of mAb



Bispecific T cell engagers[a]:

Targeting BCMA with clinical data

- CC-93269
- PF-06863135
- REGN5458
- JNJ-64007957
- AMG420

Targeting BCMA without clinical data (clinical trial open)

- TNB-383B
- AMG 701
- REGN5459

Other targets

- AMG 424
- GBR 1342
- BFCR4350A
- JNJ-64407564

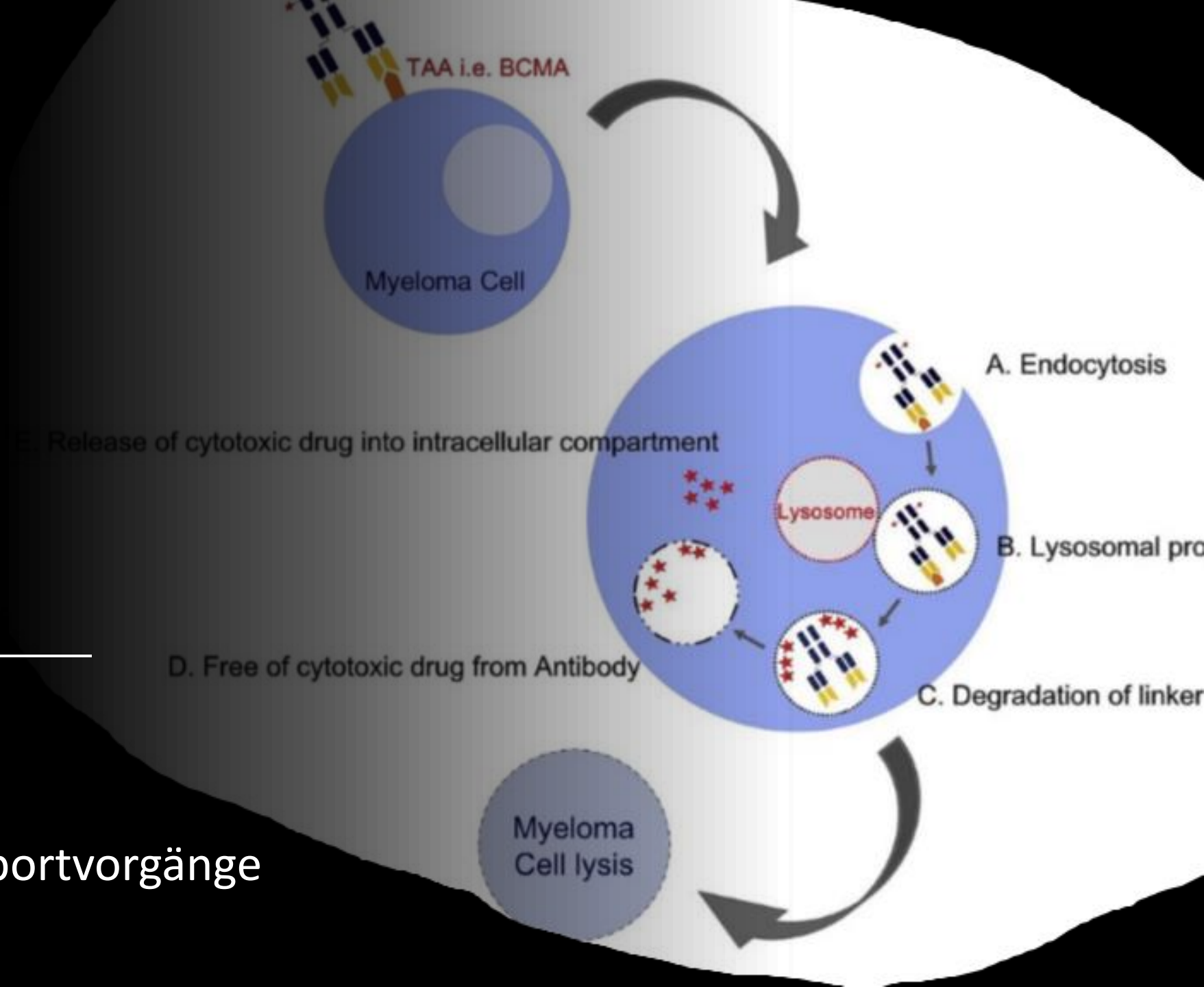
Conjugated mAb[a]:

GSK2857916: BCMA - MMAF
AMG 224: BCMA - DM1
STRO-001: CD74 - pAMF
CC-99712: BCMA ADC

[a]All the products listed are investigational only, not approved.
DM1, maytansinoid N(2')- deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine; MMAF, monomethyl auristatin F; pAMF, p-azido-methyl-phenylalanine.

1. Caraccio C, et al. Front Immunol. 2020;11:501. 2. Mackall CL, et al. Nat Rev Clin Oncol. 2014;11:693-703.
NCT03269136; NCT03933735; NCT03761108; NCT04083534; NCT03486067; NCT03145181; NCT02514239; NCT03287908; NCT03445663; NCT03275103; NCT03309111; NCT03399799; NCT03525678; NCT02561962; NCT03424603. Available from: https://clinicaltrials.gov. Accessed May 2020.

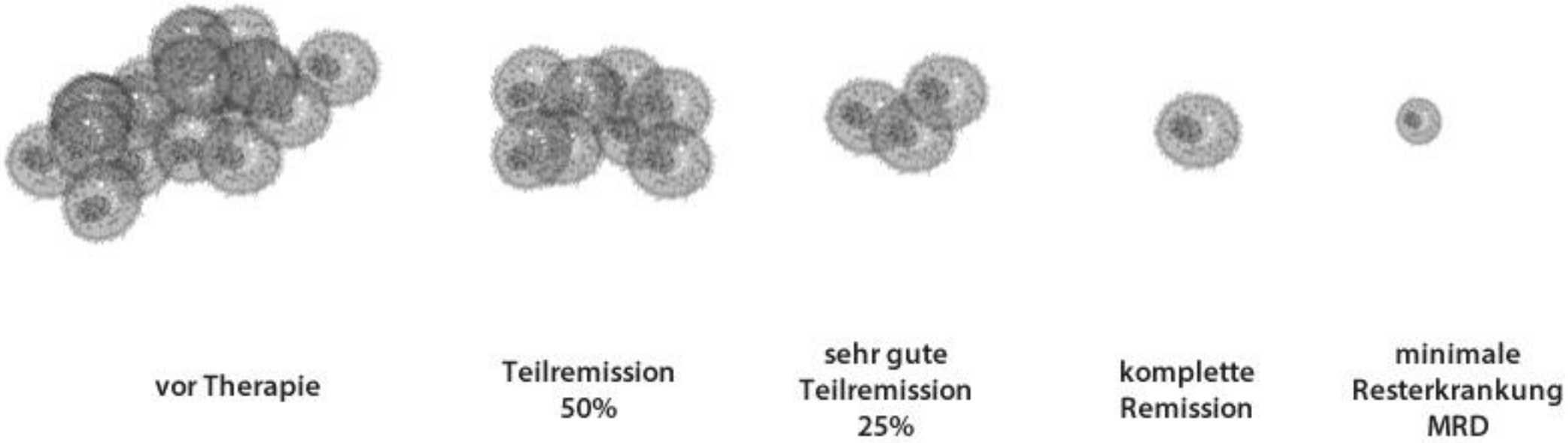
belantamab mafodotin DREAMM 2



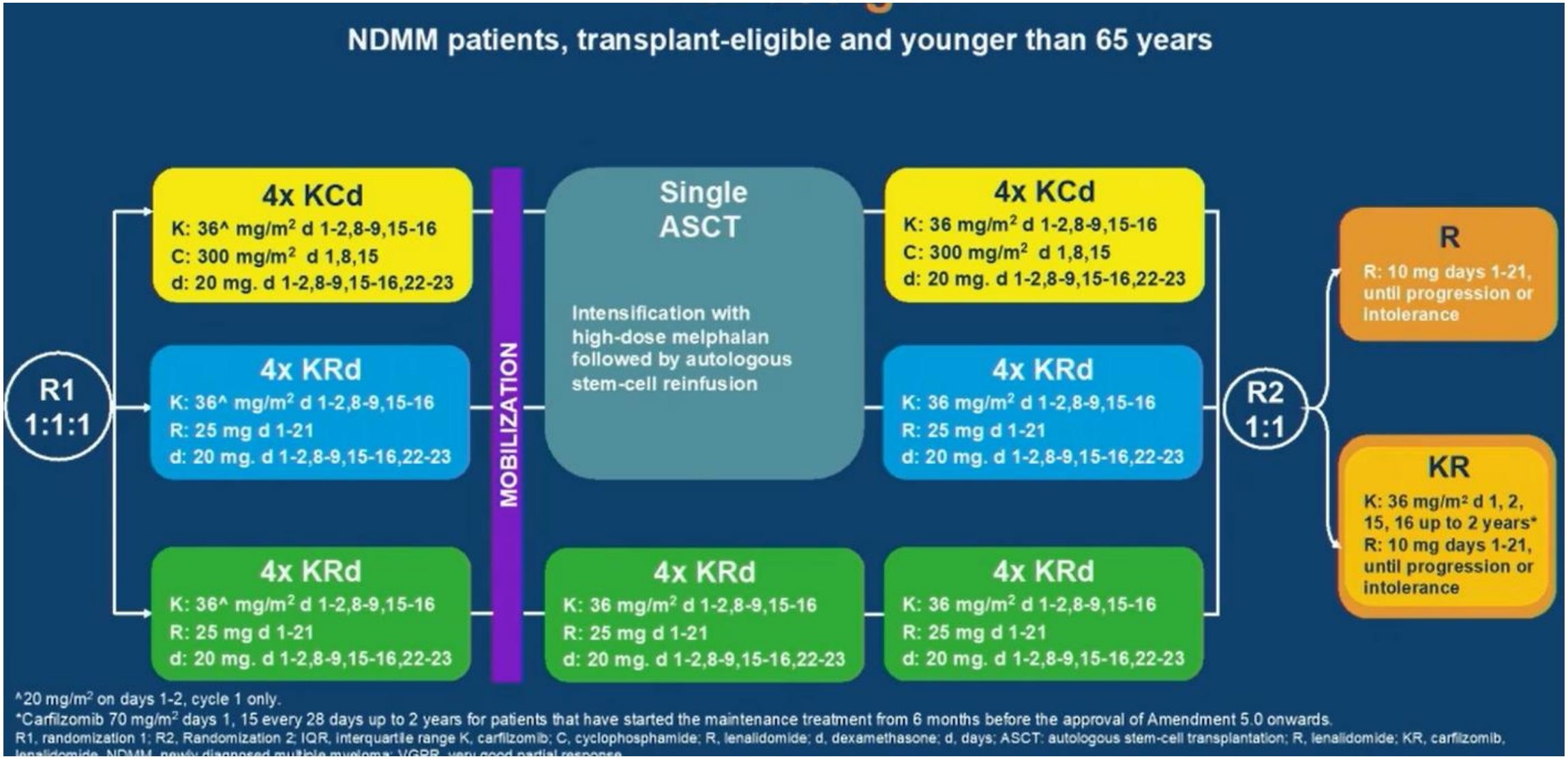
Blockade innerer Transportvorgänge

Transplantation

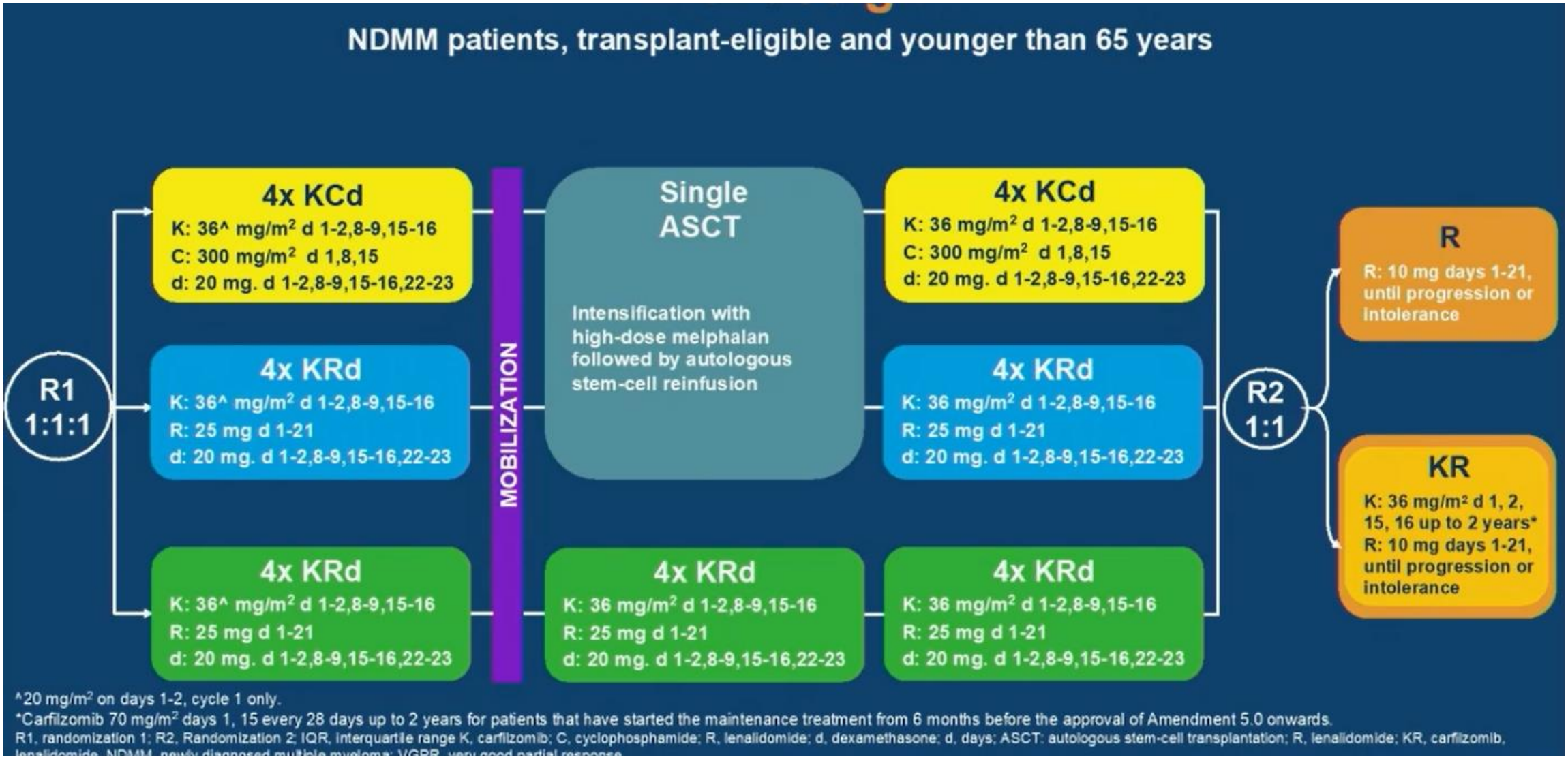
Therapieerfolg



Transplantation – ja - nein

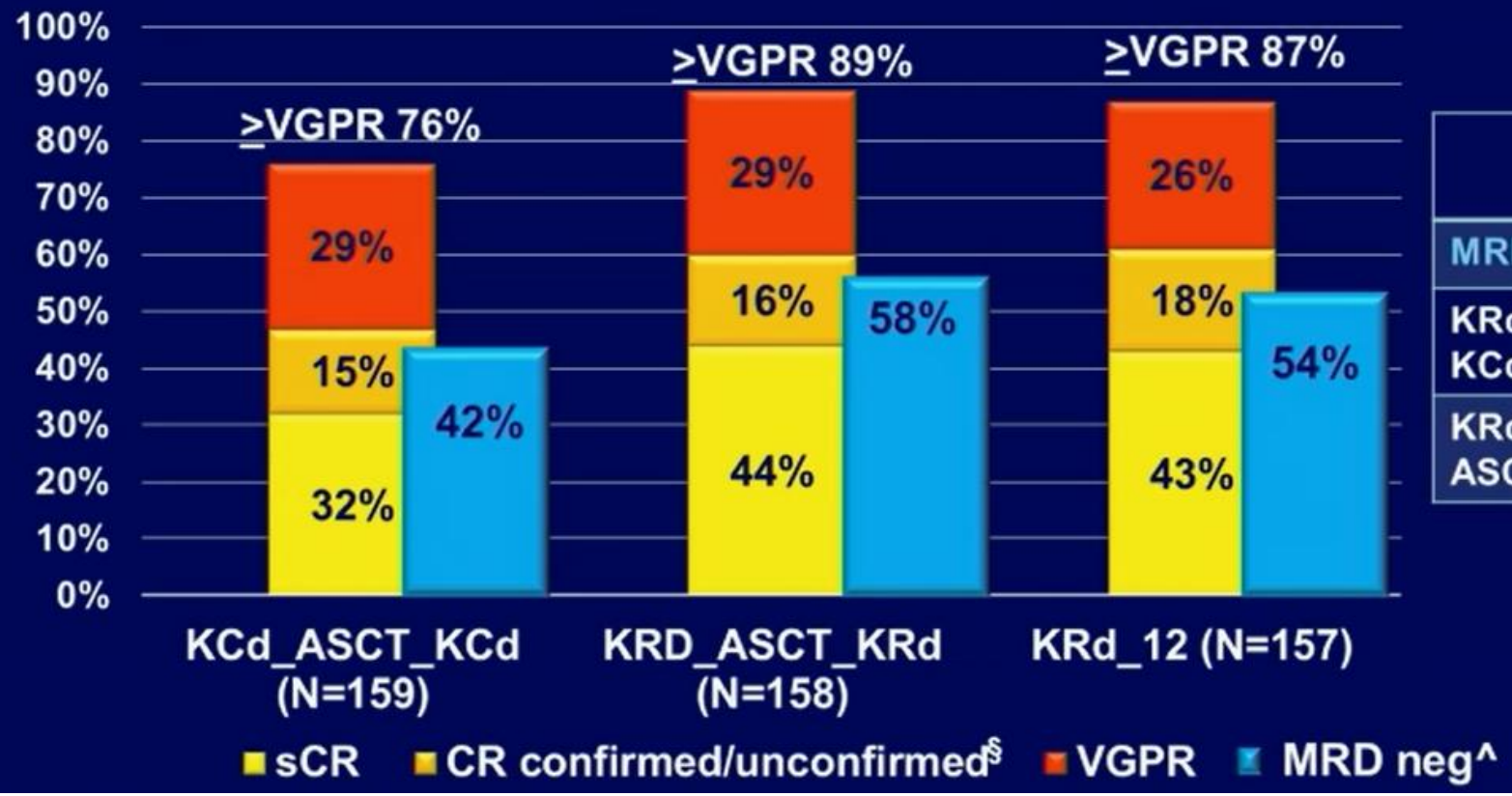


Transplantation – Konsolidierung ?



MRD Rate pre-maintenance

ITT analysis, centralized evaluation
''Second generation flow cytometry'', sensitivity 10^{-5}



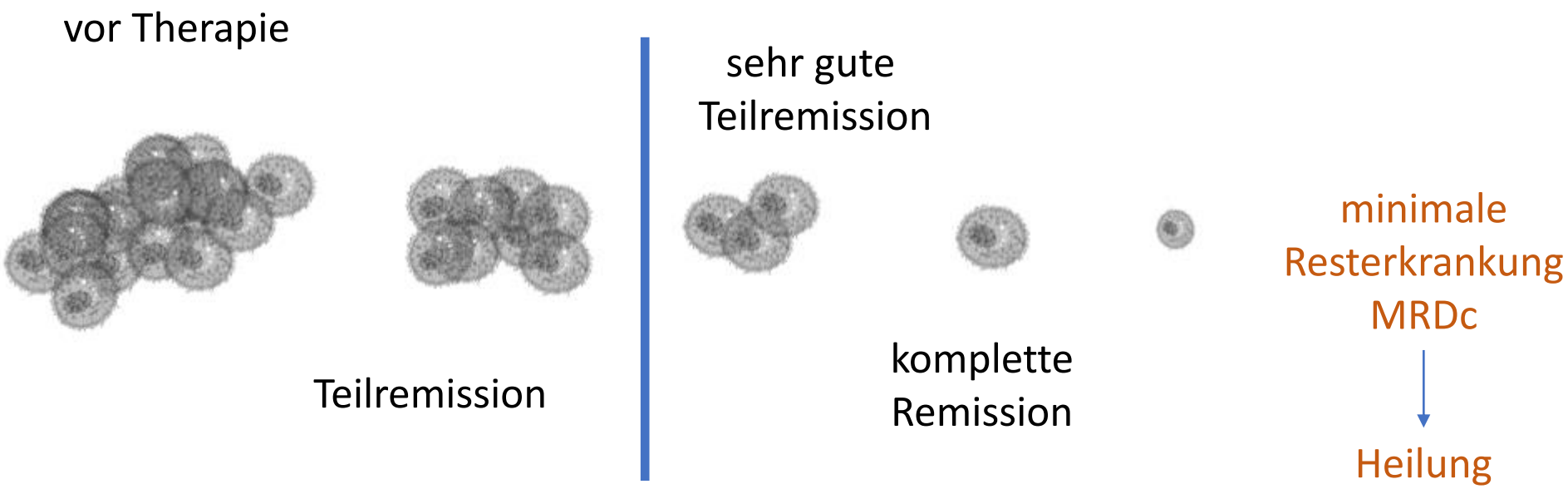
	OR	P value*
MRD neg (10^{-5})		
KRd-ASCT-KRd vs KCd-ASCT-KCd	2.02	0.009
KRd12 vs KCd-ASCT-KCd	1.73	0.042

Transplantation – ja

Therapie je länger - desto besser

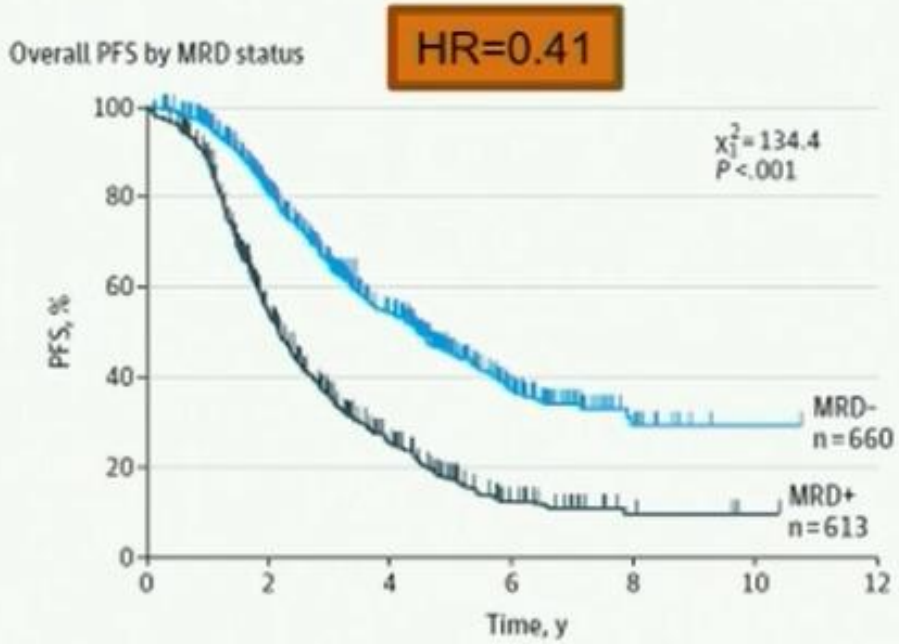
je intensiver – desto besser

MRD

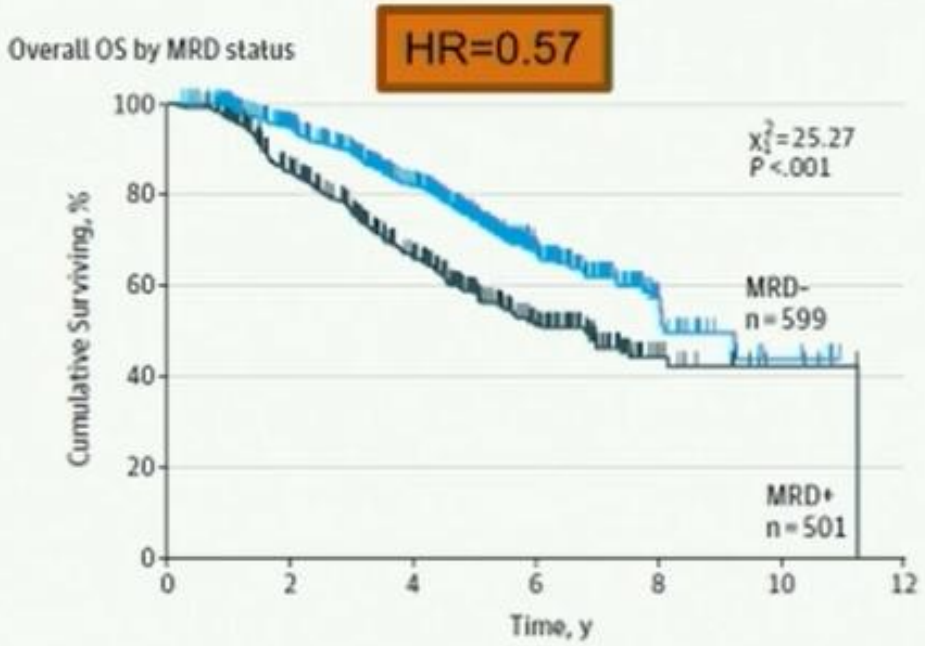

vor Therapie
Teilremission
sehr gute
Teilremission
komplette
Remission
minimale
Resterkrankung
MRDc
Heilung

Je weniger – desto besser

- ✓ **21 studies that reported PFS or OS in 20 or more patients following treatment for multiple myeloma**
- ✓ **14 studies (n=1273 patients) and 12 studies (n=1100 patients) provided data on PFS and OS, respectively.**

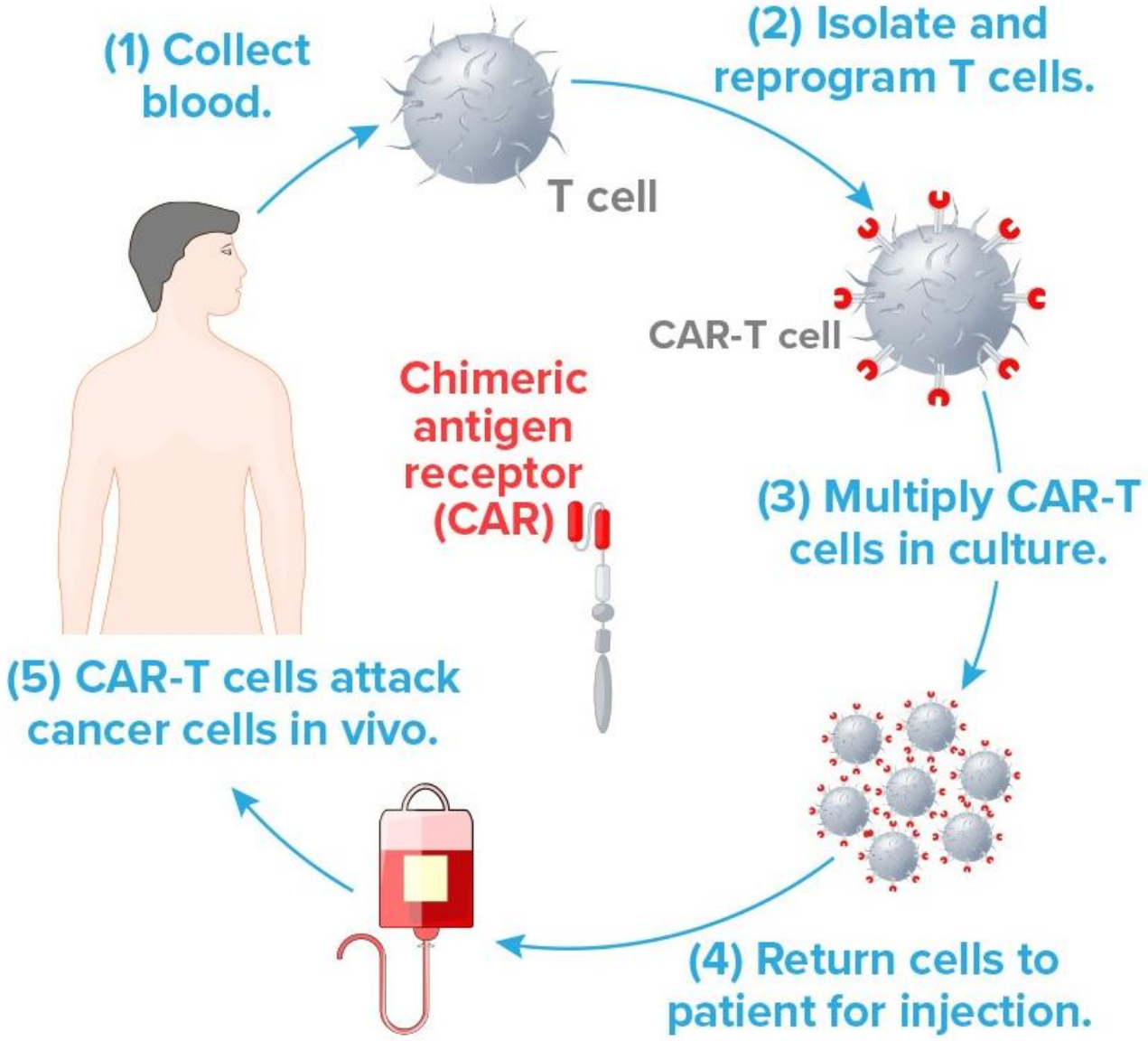


No. at risk					
MRD -VE	457	214	70	12	1
MRD +VE	308	113	28	4	1

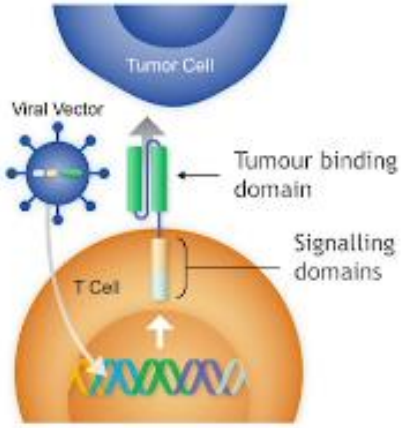


No. at risk					
MRD -VE	508	359	139	26	4
MRD +VE	390	250	105	17	5

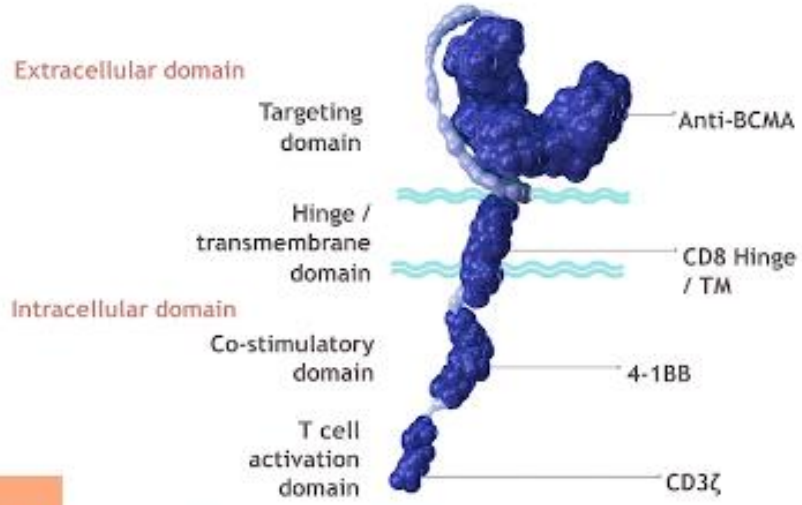
CAR T Zellen


(1) Collect blood.
T cell
(2) Isolate and reprogram T cells.
CAR-T cell
Chimeric antigen receptor (CAR)
(3) Multiply CAR-T cells in culture.
(4) Return cells to patient for injection.
(5) CAR-T cells attack cancer cells in vivo.

Idecabtagene vicleucel (ide-cel) BCMA CAR T cell: construct design



Ide-cel CAR design



Ide-cel is a 2nd-generation CAR construct

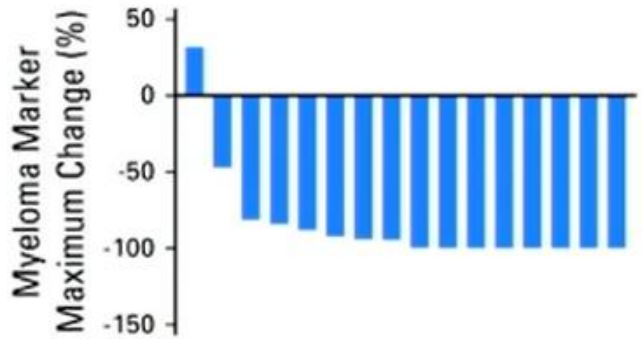
- Autologous T cells transduced with a lentiviral vector encoding CAR specific for human BCMA
- Targeting domain: **anti-BCMA**
- Co-stimulatory domain: **4-1BB**
- T cell activation domain: **CD3-zeta**

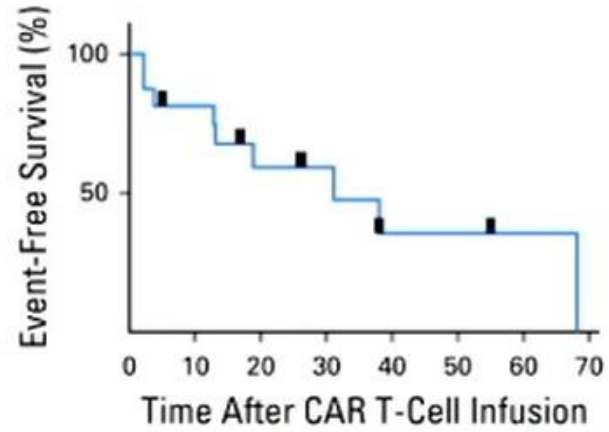
Ide-cel is investigational only, not approved.

1. Ali SI, et al. Blood. 2016;128:1688-700. 2. Raje N, et al. NEJM. 2019;380:1726-37.

Updated NCI results

- 16 patients treated at 9 x 10^6 cells/kg
- Median prior lines: 9.5
- ORR: 81%
- ≥VGPR: 63%
- EFS 31 weeks





hohe Ansprechraten

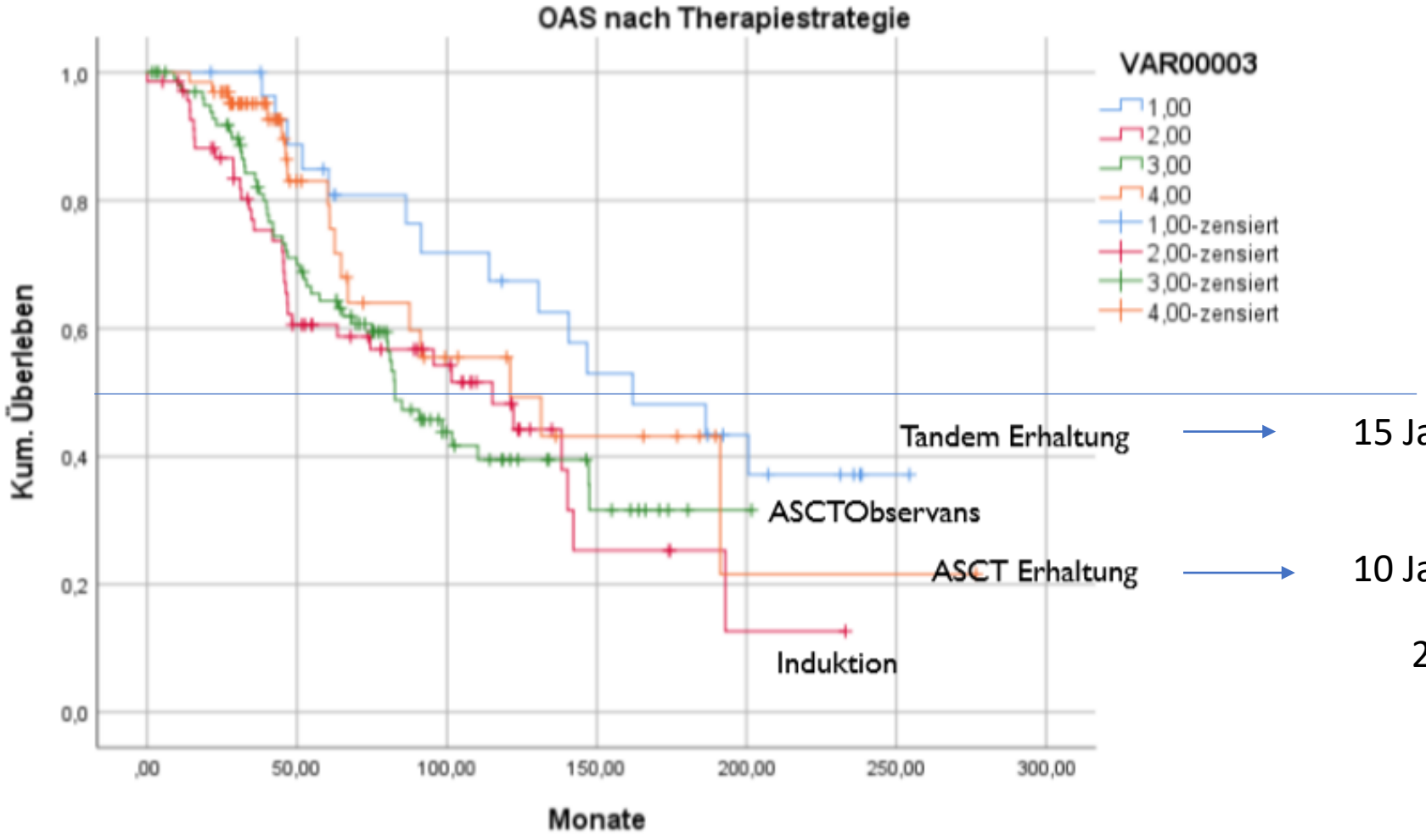
keine Heilung

T Zellen bis 16 Monate nachweisbar

nach dem Verschwinden - Rückfall

Graz

OAS – Vergleich der Strategien



15 Jahre 50% am Leben

10 Jahre 50% am Leben

20 – 30% geheilt