Multiples Myelom: Welche Immuntherapie für dreifach-exponierte Patienten?

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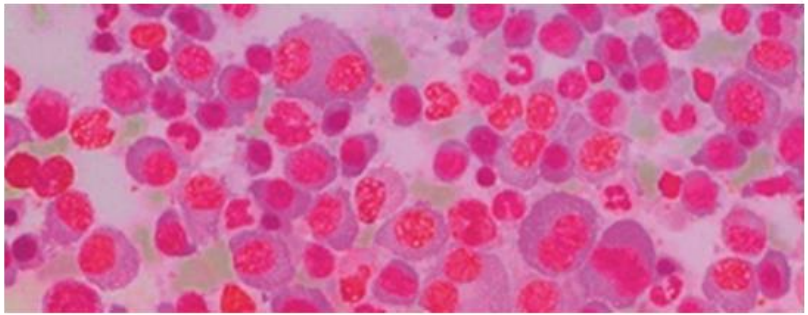


Sonntag 13.10.2024

Offenlegung potentieller Interessenkonflikte

1. Anstellungsverhältnis oder Führungsposition

keine

2. Beratungstätigkeit

Amgen, BMS, GSK, Janssen, Pfizer, Sanofi, Stemline, Takeda

3. Aktienbesitz

keiner

4. Honorare

keine

5. Finanzierung wissenschaftlicher Untersuchungen

Clinical trial grant support: BMS, Janssen, Pfizer

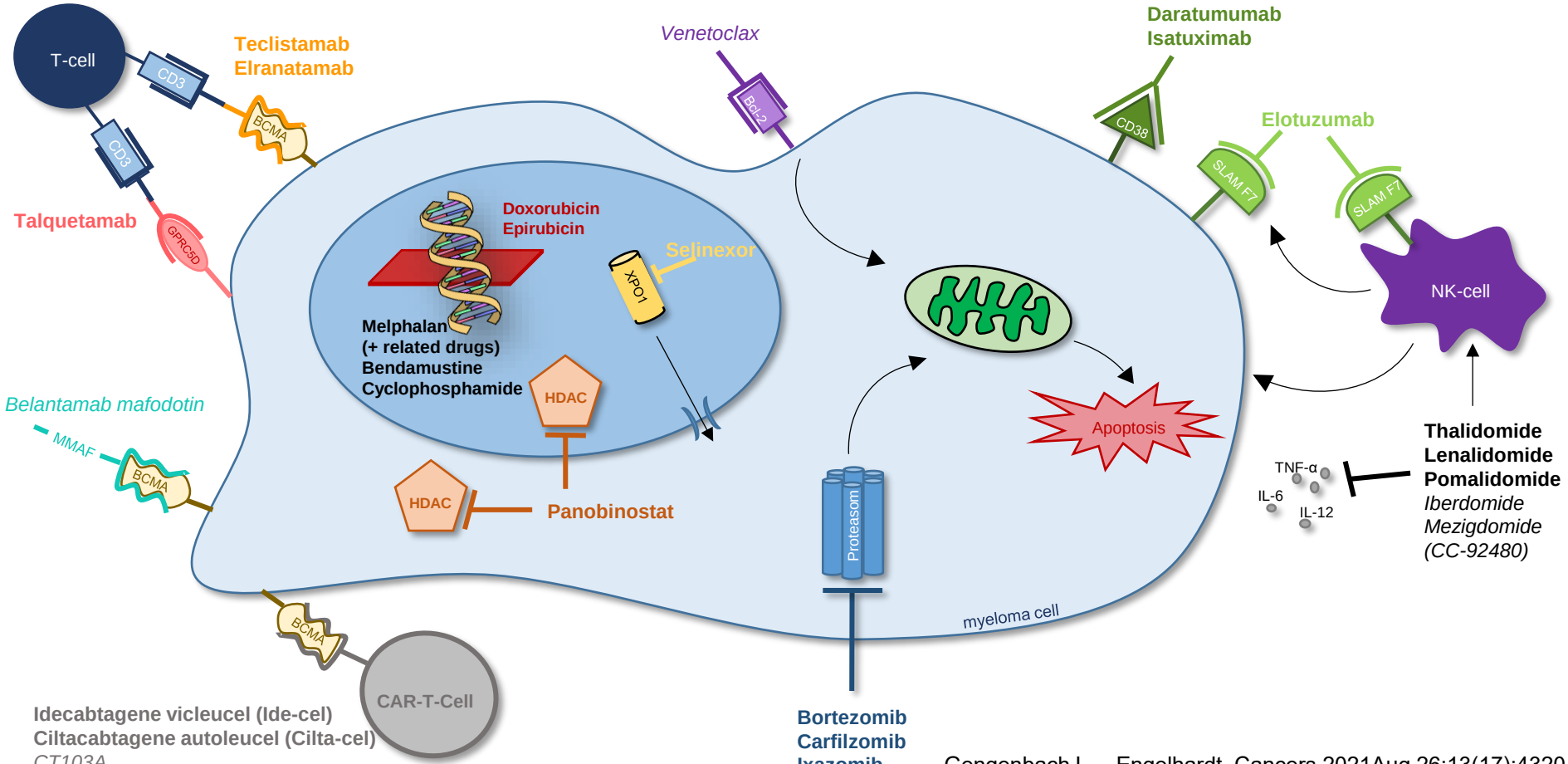
6. Gutachtertätigkeit

keine

7. Andere finanzielle Beziehungen

keine

Mögliche Medikamente beim Multiplen Myelom

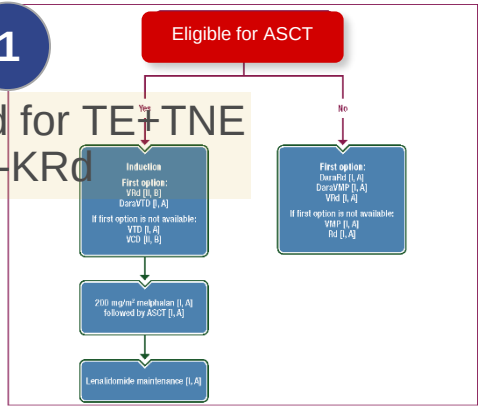


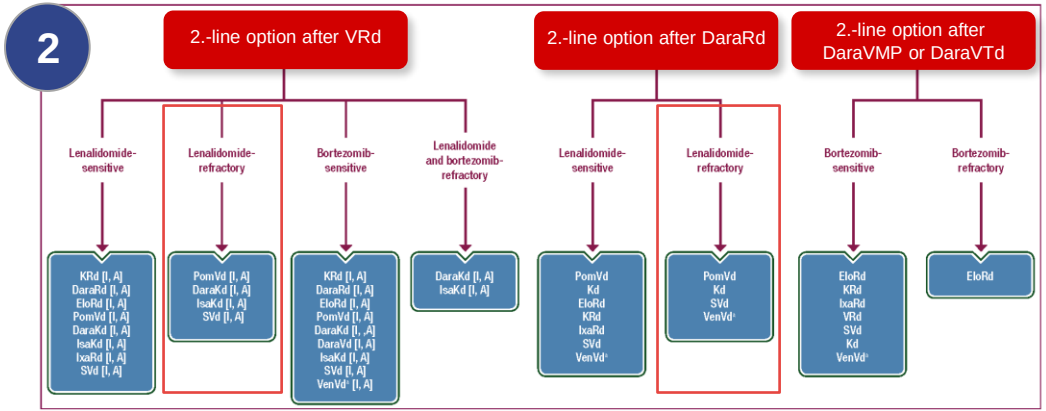
Gengenbach L,…Engelhardt. Cancers 2021Aug 26;13(17):4320
Klinische Leitlinie MM. Deutsches Ärzteblatt 14;2022

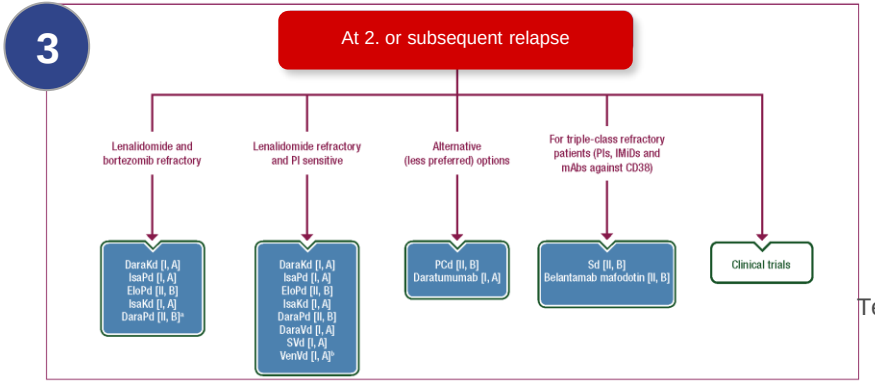
Kursiv: noch nicht od. nicht mehr zugelassen

Internationale Leitlinien für 1., 2. + 3.Linientherapien

CD38-VRd for TE+TNE
HR: CD38-KRd







- CAR-Ts
- BiTEs
- ADC
- Celmods
- + other study agents missing

Terpos et al. EHA-EMN guideline renewed, 2024/25 expected
Kortüm et al. Onkopedia MM update 2024/25

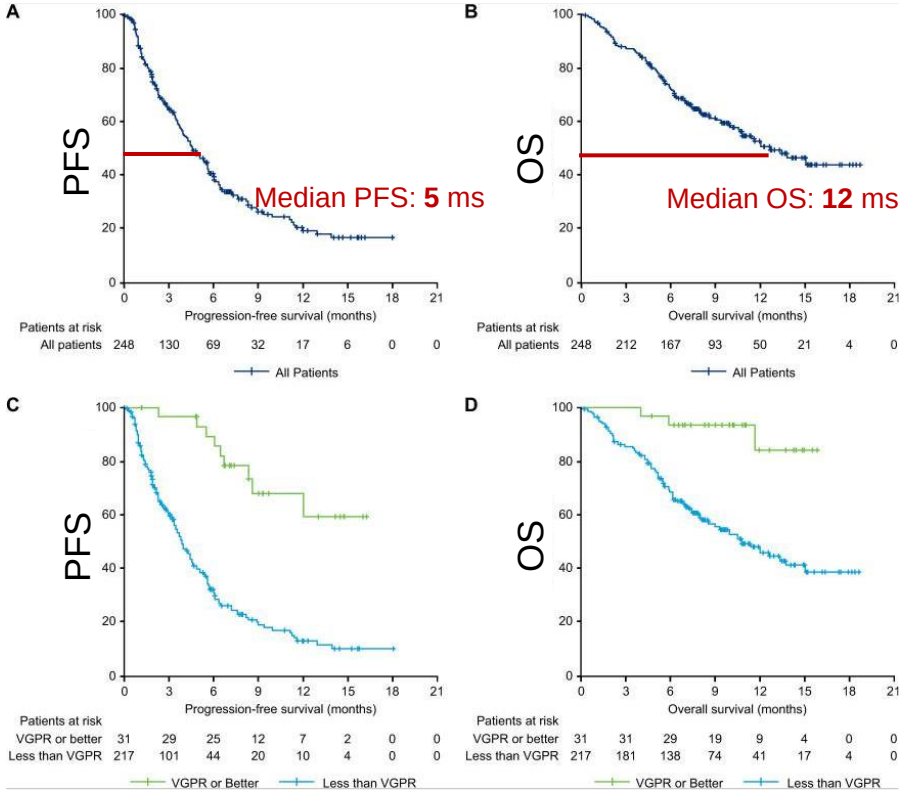
Dimopoulos MA et al. Ann Oncol 2021;32:309-3220

Some combos are not licensed in EU

LocoMMotion: prospective, non-interventional, multinational study: real life standards in RRMM pts ≥3 prior lines of therapy

Triple-class (PI, IMiD, CD38-Ab) exposed RRMM pts (n=248),
92 varied regimens, no clear SOC for heavily pretreated TCE RRMM
ORR: 30%, median PFS: 5 + OS: 12 ms
Treatment-emergent AEs: 84% (G 3/4: 53%)
107 deaths: PD (n=74, 69%)

SOC treatment, *n* (%)[a]	*N* = 248
Glucocorticoid	220 (88.7)
PI	133 (53.6)
Carfilzomib	63 (25.4)
Bortezomib	48 (19.4)
Ixazomib	22 (8.9)
IMiD	117 (47.2)
Pomalidomide	74 (29.8)
Lenalidomide	36 (14.5)
Thalidomide	7 (2.8)
Alkylating agent	107 (43.1)
Cyclophosphamide	79 (31.9)
Bendamustine	16 (6.5)
Melphalan	15 (6.0)
Anti-CD38 monoclonal antibody	24 (9.7)
Daratumumab	23 (9.3)
Isatuximab	1 (0.4)
Anthracyclines	18 (7.3)
Topoisomerase inhibitor	16 (6.5)
Other antineoplastic agent[b]	15 (6.0)
Histone deacetylase inhibitor	12 (4.8)
Anti-SLAMF7 monoclonal antibody	9 (3.6)
BCMA-targeted antibody-drug conjugate	7 (2.8)
Bcl-2 inhibitor	6 (2.4)
Autologous stem cell transplant	6 (2.4)
Mitotic inhibitor	2 (0.8)
Selective inhibitor of nuclear export	2 (0.8)



Mateos MV. Leukemia 2022;36:1371-6
Ihorst,…Engelhardt et al. Analysis of survival by tumor response: have we learnt any better? AnnHematol 2015;94:1615-6

IgG kappa MM with LCDD, 53 yrs, ♂

IgG k - MM
light-chain deposition disease (LCDD)
ISS 2, R-ISS 2, CRAB: 2/4, BM: 20% PCs, CG: unfavorable (1q21, del14q32),
Fit

2024

Performed therapies	Treatment regimens
1.LT	Dara-VRd -> ASCT + maintenance -> TCE
2.LT upon 1.PD	Kd or CD38-Kd -> 4-drug exposed
3. LT	?

9.5ys (112 ms) from ID to 5.LT

What treatment next?

1. Sel-Vd or other SOC
2. 2. Re-ASCT 9 yrs after 1.ASCT
3. Allo-SCT due to young age and fit patient[3,4]
4. BiTE (ahead of CAR-T)
5. CAR-T-cells[5] (before possibly later BiTE) ?

1. Einsele H, Engelhardt M et al. Br J Haematol. 2017;179:586
2. Bachmann, Schreder, Engelhardt et al. Cancers. 2021;13:1322
3. Greil. Haematologica. 2019;104:370, 4. Greil, Engelhardt, Finke, Wäsch. Cancers. 2021;14:55
5. Wäsch R,…..Engelhardt M. Ann Hematol 2023

Slide provided by the speaker based on clinical experience.

BCMA-targeting therapies (cell therapies and bispecifics)

2L+	3L+ RRMM	4L+ RRMM
Min. double-class exposed (Len, PI) and Len-refractory	*Min. TCE (IMiD, PI, CD38)*	*Prior TCE*

Ide-cel

KarMMa-3[1], Ph 3
(ide-cel vs standard regimens)
2–4 prior regimens with mAb, PI, IMiD agent

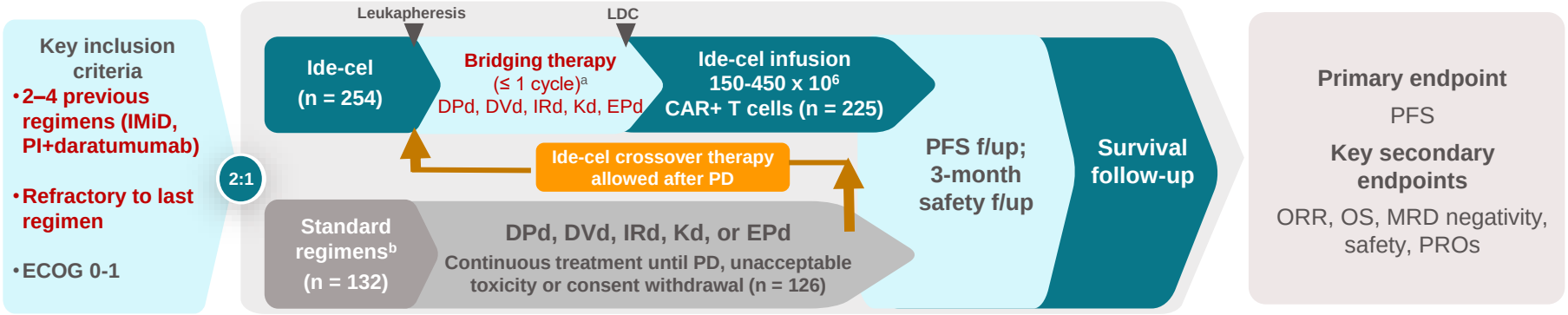
Cilta-cel

CARTITUDE-4[2], Ph 3
(PVd or DPd vs cilta-cel)
1–3 prior regimens with PI and IMiD agent

Bispecifics & T-cell engager

1. Rodriguez-Otero P. N Engl J Med. 2023;388:1002
2. San Miguel, J. N Engl J Med. 2023;389:335

KarMMa-3: Ide-cel vs SOC in pts w TCE RRMM after 2–4 prior LOT

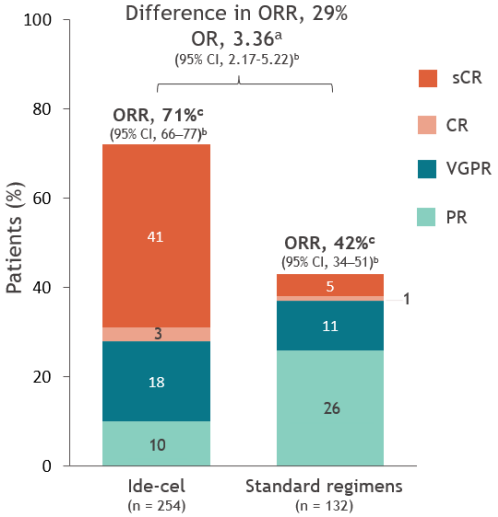


Characteristics	Ide-cel (n = 254)	SoC (n = 132)
Age, median (range), years	63 (30–81)	63 (42–83)
Median time from diagnosis to screening, years (range)	4.1 (0.6–21.8)	4.0 (0.7–17.7)
Median prior regimens	3 (2–4)	3 (2–4)
EMD, n (%)	61 (24)	32 (24)
High tumor burden, n (%)	71 (28)	34 (26)
High-risk cytogenetics, n (%)[d] / Ultra-high risk	166 (65) / 67 (26)	82 (62) / 29 (22)
Previous autologous HSCT, n (%)	214 (84)	114 (86)
Daratumumab refractory, n (%)	242 (95)	123 (93)
TCR, n (%)	164 (65)	89 (67)

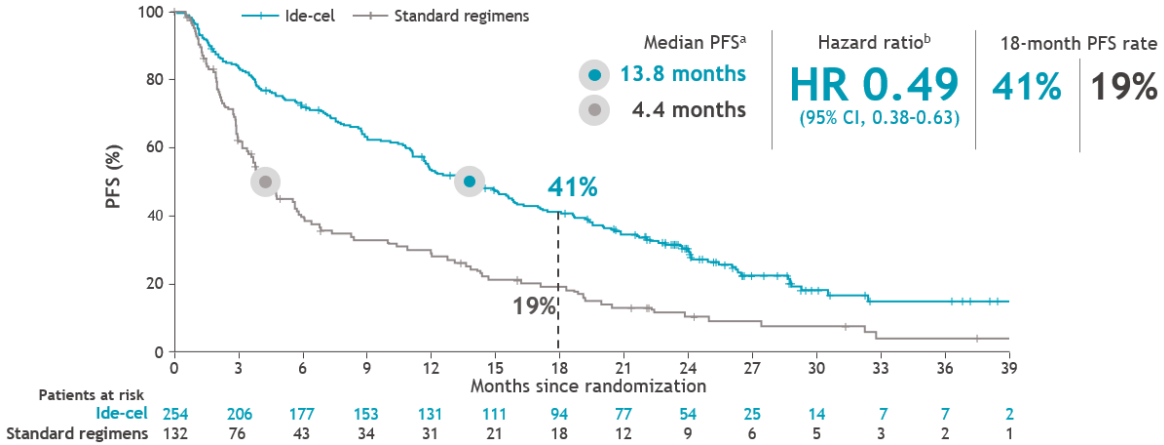
Rodriguez-Otero P. N Engl J Med. 2023;388:1002

KarMMa-3: Benefit with ide-cel for ORR and PFS in TCE RRMM pts

Response



PFS (ITT)



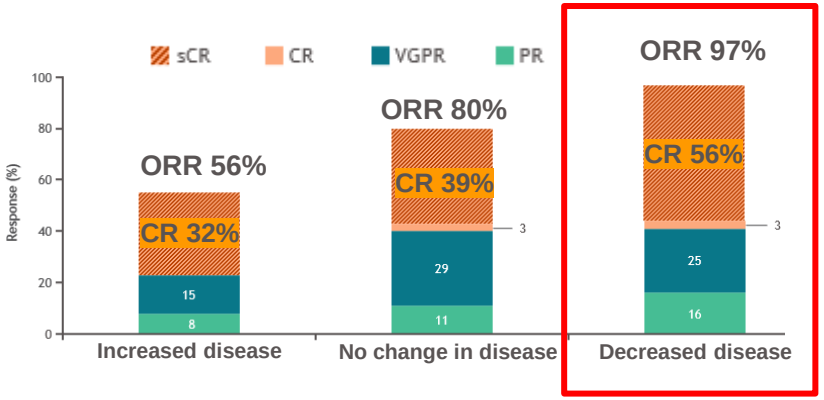
Median follow-up: 30.9 months

Secondary endpoint	Ide-cel (n = 254)	Standard regimens (n = 132)
CR rate (95 % CI), %[d]	44 (38-50)	5 (2-9)
MRD-negative CR rate, n/N (%) (95% CI)[e]	57/163 (35) (28-42)	1/54 (2) (0-5)
Median (95% CI) DOR, months	16.6 (12.1-19.6)	9.7 (5.5-16.1)
Median PFS2, months	23.5	16.7
HR (95% CI)	0.79 (0.60-1.04)	

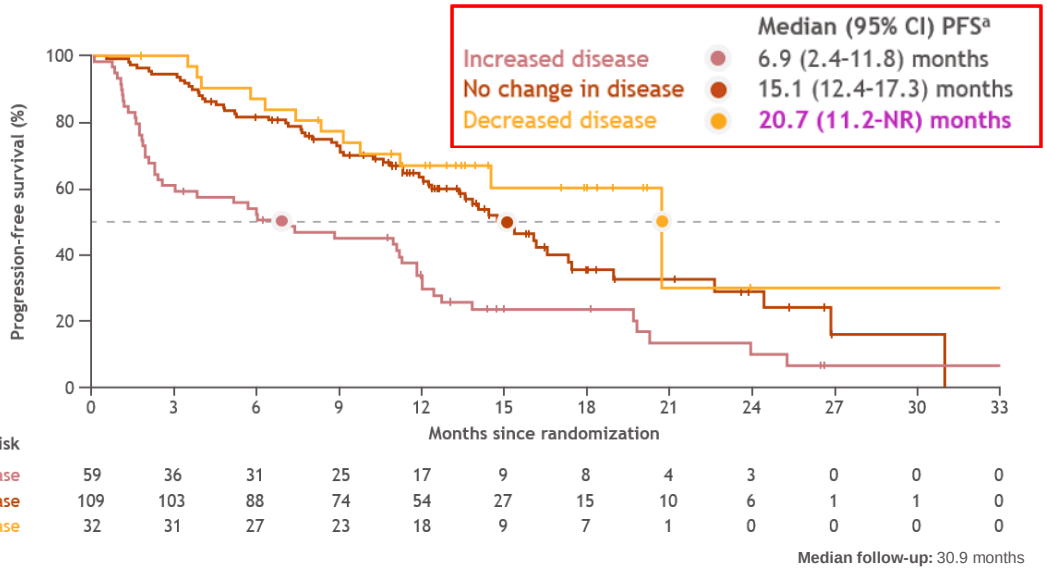
Rodriguez-Otero P et al. ASH 2023, [oral #1028]

KarMMa-3: Impact of bridging on ide-cel

Response of ide-cel post bridging



PFS of ide-cel post bridging

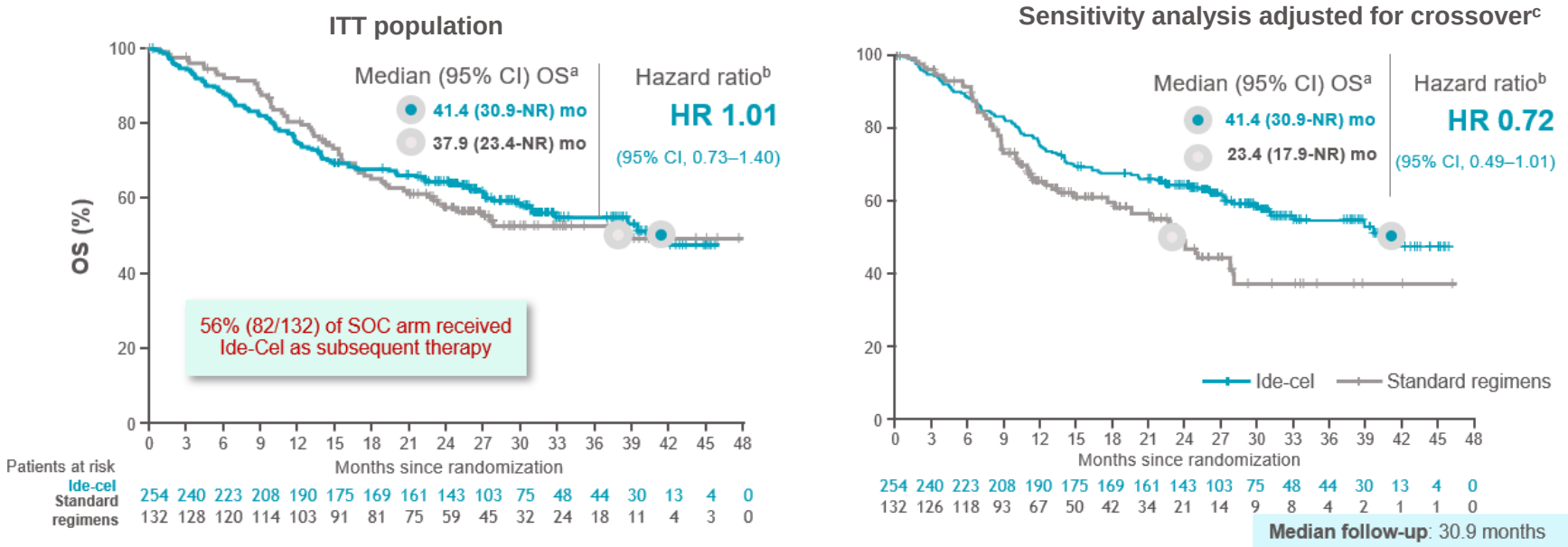


Median follow-up: 30.9 months

Ide-cel with effective bridging increased ORR to 97% and CRR to 56% -> associated with prolonged PFS of 20.7 mos

Einsele, et al. IMS 2023. [Poster P-008]

KarMMa-3: OS analysis confounded by substantial crossover



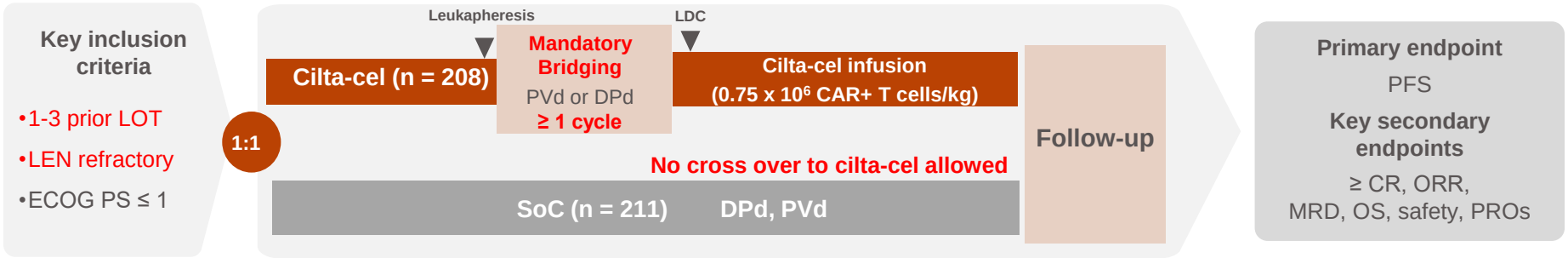
Consistent safety profile with ide-cel

- No new safety signals
- No new CRS or iiNT events with ide-cel with 30.9 months follow-up
- No parkinsonism or Guillain-Barré syndrome reported in KarMMa-3
- No SPMs of T-cell origin in the ide-cel arm

Information fraction for OS was 74% (n = 164/222 required events). a) Based on Kaplan–Meier approach; b) Stratified HR is based on the univariate Cox proportional hazards model. CI is 2-sided and calculated by bootstrap method; c) Two-stage Weibull model without recensoring (prespecified analysis). NR, not reached.

Rodriguez-Otero P, et al. ASH 2023. [oral #1028]

CARTITUDE-4: Cilta-cel in pts w LEN-refr. RRMM after 1–3 prior regimens

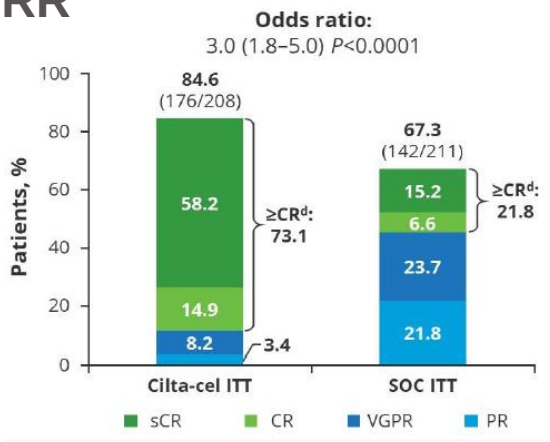


Characteristics	Cilta-cel (n = 208) - ITT	SoC (n = 211) - ITT
Age, median (range), years	61.5 (27–78)	61.0 (35–80)
Median time since diagnoses, years (range)	3.0 (0.3–18.1)	3.4 (0.4–22.1)
Median number of prior regimens	2 (1-3)	2 (1-3)
High-risk cytogenetics, n (%) With ≥ 2 high-risk abnormalities	123 (59.4) 43 (20.8)	132 (62.9) 49 (23.3)
Triple-class exposure, n (%)	53 (25.5)	55 (26.1)
Daratumumab refractory, n (%)	48 (23.1)	45 (21.3)
Triple-class refractory, n (%)[b]	30 (14.4)	33 (15.6)

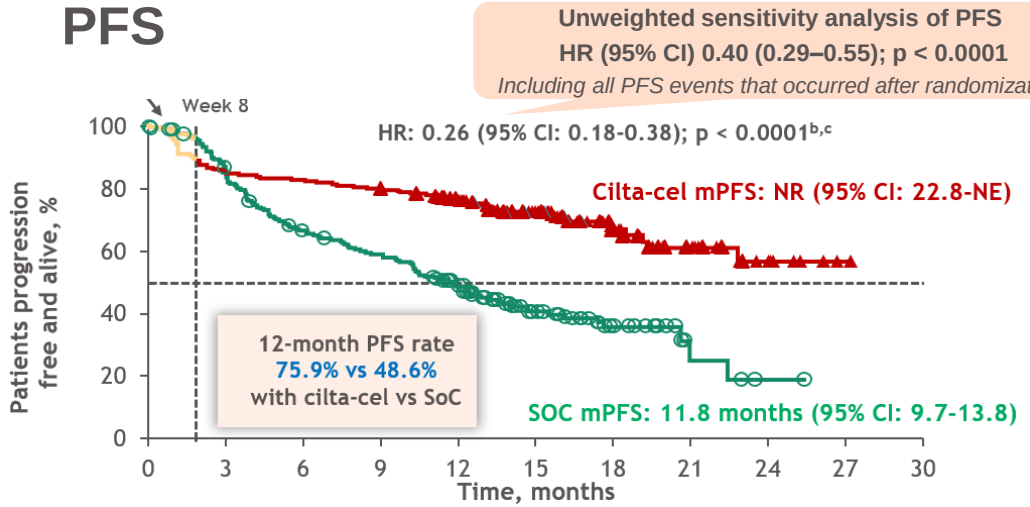
Dhakal B, et al. J Clin Oncol 2023;41(17 Suppl). Abstract LBA106; San-Miguel J, et al. N Engl J Med 2023;389:335–347

CARTITUDE-4[2,3]: Cilta-cel in pts w LEN-refr. RRMM after 1–3 prior regimens

ORR



PFS



KarMMa-3[1]
100% TCE

Ide-cel vs. KPd, DVd, IRd, Kd, EPd

Bridging optional: ≤1 cycle

Cross-over to Ide-cel allowed

IMID+ PI+ CD38-ab

Cartitude-4[2,3]
Double-exposed: Len+PI; 26TCE

Cilta-cel vs. PVd, DPd

Bridging mandatory: ≥1 cycle

Ø cross-over to Cilta-cel allowed

Selection of criteria for illustrative purposes

Moving ahead:
- KarMMa-2: Ide-cel in multiple exploratory cohorts
- Cartitude-2: Cilta-cel in multiple exploratory cohorts
- Cartitude 5+6: Cilta-cel in TNE+TE NDMM vs. Len + vs. Tx

1. Rodriguez-Otero P. N Engl J Med. 2023;388:1002
2. San Miguel, J. N Engl J Med. 2023;389:335
3. Dhakal B, et al. JCO 2023;41.LBA106

Summary of approved TCE/bispecifics in 4L+ RRMM

	Teclistamab (BCMA-CD3) MajesTEC-1 [a,b]	Elranatamab (BCMA-CD3) MagnetisMM-3 [c,d,e]	Talquetamab (GPRC5D-CD3) Monumen-TAL-1 [f,g] 400µg/kg sc QW / 800µg/kg sc Q2W
Follow-up, median	30.4 months [b]	17.6 months [c]	29.8 /23.4 months [f]
Patients, number	165	123	143 / 154
Median prior regimens	**5**	**5**	**5/6**
Triple refractory, %	128 (78%)	123 (100%)	73%/ 69%
ORR, % (@ effective dose)	**63% (1.5mg kg/KG)**	**61% (≥215 µg/kg)**	**74% / 70% (400/800 µg/kg)**
≥ CR, %	46%	37%	33% / 40%
mPFS, months	11.4 (8.8-16.4)	17.2 (9.8-NE)	7.5 (5.7-9.4) / 11.2 (8.4-14.6)
mOS, months	22.2 (15.1- 29.9)	24.6 (13.4-NE)	24 mo OS: 61% / 67%
CRS (all grades), %	119 (72%)	48 (87%)	79% / 75%
CRS grade 3/4, %	0.6%	0	2.1% / 0.7%
NT / ICANS, %	14.5% / 3%	3%	11% / 11%
Infection all, (grade 3/4), %	79% (55%)	70% (40%)	61% / 70% (22% / 20%)

Presentation contains selection of studies for descriptive purposes. Direct study comparison is inappropriate due to differences in trial design, methods and patient populations

a. Moreau et al, N Engl J Med 2022;387:495; b. Oriol et al, presented @ EHA 2024, #942; c. Mohty et al, presented @ EHA 2024, #932; d. Tomasson et al, presented @ ASH 2023, #3385; e. Lesokhin et al. Nat. Med. 2023;29:2259. f. Schinke et al, presented @ ASCO 2023, #8036; g. Rasche et al, presented @ EHA 2024, #915; NE- not evaluable; mo = months, m = median; ORR = overall response rate, CRR = complete remission rate; PFS = progression free survival; OS = overall survival, CRS cytokine release syndrome

Use of bispecific antibodies after CAR T therapy

	Teclistamab[1,2] MajesTEC-1		Teclistamab[3] RWE (5 US sites)		Elranatamab[4,5] MagnetisMM-3		Talquetamab[6,7] MonumenTAL-1		Bispecific Antibodies[8c] RWE (Mayo clinic)	
	Total population (n=165)	Prior CAR T (n=15)	Total population (n=104)	Prior CAR T (n=33)	Total population (n=123)	Prior CAR T[a] (n=36)	Total population[b] (n=143/145)	Prior CAR T (n=23)	No prior CAR T (n=34)	Prior CAR T (n=28)
ORR	63.0%	53.3%	66%	57%	61.0%	52.8%	74%/70%	72.9%	52.9%	50.0%
CR	45.5%	26.7%	29%	29%	37.4%	19.4%	32.9%/40.3%	45.8%	14.7%	25.0%

These therapies have not been compared in a head-to-head clinical trial, and direct comparisons should not be made between therapies

Irrespective of prior CAR-T exposure, bispecific antibodies can be clinically active for MM pts

a) Pooled from 4 MagnetisMM Studies b) 0.4 mg/kg SC QW / 0.8 mg/kg SC Q2W c) 77.4% were treated with Teclistamab and 22.6% with Talquetamab

1.Touzeau C, et al. EHA 2022. [Oral S184]. 2. Sidana S, et al. EHA 2023. [Poster #879]. 3. Dima D, et al. ASH 2023. [oral 91]. 4. Mohty M, et al. EHA 2024. [Poster #P932]. 5. Nooka A, et al. EHA 2023. [Poster #870]. 6. Rasche R, et al. EHA, 2024 [Poster #915]. 7.Jakubowiak A, et al. ASH 2023. [Poster #3377]. 8. Bansal R,et al. EHA 2024 [Poster #7520]

Ide-cel in IgG kappa MM with LCDD, 53 yrs, ♂

IgGk- MM, ID 4/2013, light-chain deposition disease (LCDD) -> renal impairment (RI), ISS 2, R-ISS 2, CRAB: 2/4, CG: unfavorable (1q21, del14q32), BM: 20% PCs

Time	Performed therapies	Treatment regimens	Response
5/2014	1.LT	VCD, CE+ASCT -> Vd-maintenance[1,2]	VGPR
6/2019	2.LT upon 1.PD	Daratumumab-Vd	PR -> PD
1/2021	3.LT upon 2.PD	Elotuzumab-Pd	PR -> PD
5/2023	4.LT upon 3.PD	Kd	SD -> PD
9/2023	**5.LT**	**Ide-cel CAR-T-cells; cond. Flu/Cy[3]**	**CR ongoing**

9.5ys (112 ms) from ID to CAR-Ts

Challenges: None, approval health insurance despite RI; only CRS grade 1 -> Ø tocilizumab

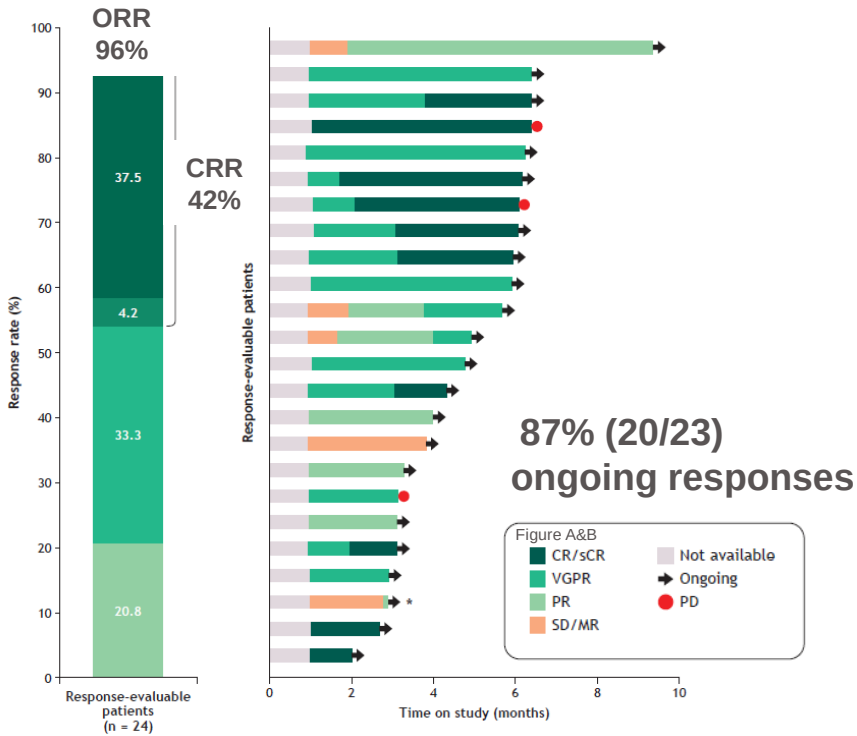
Advantages: no subsequent anti-MM post CAR-Ts -> treatment-free interval -> QoL ↑

Slide provided by the speaker based on clinical experience.

1 Einsele H, Engelhardt M et al. Br J Haematol. 2017;179:586
2 Bachmann, Schreder, Engelhardt et al. Cancers. 2021;13:1322
3 Wäsch R,…Engelhardt M. Ann Hematol 2023

GPRC5D CAR-T cell therapy FIH study: CC-95266-MM-001, cohort c in patients with 1 to 3 prior MM regimens

Responses (ORR) over time



Treatment related AE of interest

TRAE of interest, n (%)	All treated patients (N = 31) Any grade	Grade 3/4
ICANS[a]	3 (10)	0
NINT[b]	1 (3)	0
Select on-target/off-tumor AEs of skin, nails, mouth		
Dysgeusia	9 (29)	0
Nails[c]	8 (26)	0
Skin[d]	3 (10)	0
Dysphagia	2 (6)	0
Other AEs suspected related to BMS-986393		
Weight loss	1 (3)	0

- ICANS median onset was 5 days (range 4–6) with a median duration of 2 days (range 2–2)
- One pt experienced treatment-related non-ICANS-type neurotoxicity (NINT) (grade 2 ataxia)
- On-target/off-tumor TEAEs were reported in 18 pts (58%), and TRAEs in 15 pts (48%); all were grade 1/2

Median follow-up for all treated pts was 4.9 mo (range, 2.0 -9.3); Treated with Recommended Phase 2 dose (RP2D) 150x10^6 CAR T cells

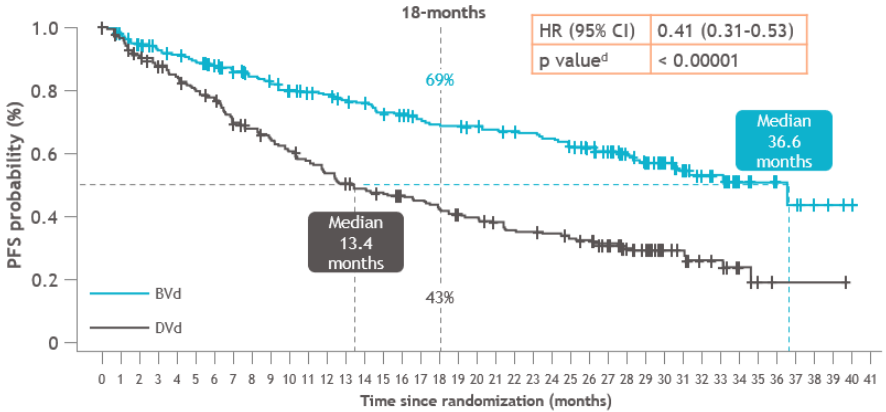
The mentioned agent/combinations are under investigation and have not been approved by any regulatory authority

Nadeem O. et al, EHA 2024, P951

Antibody-Drug Conjugate: Belantamab Mafodotin Combinations in RRMM

DREAMM-7: BVd vs DVd

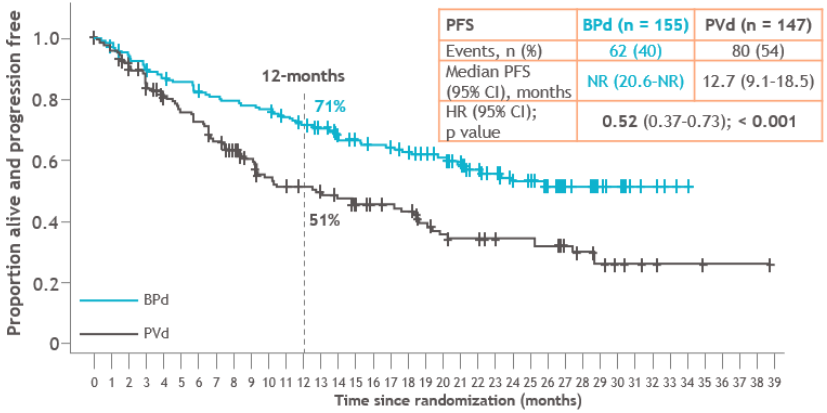
494 pts after a median of 1PL
Len exp/ref: 52%/34%



- ORR: 83% vs 71%; CR rate: 34% vs 17%
- MRD-ve rate: 39% vs 17%, early benefit in OS as well as DoR
- G3-4 thrombocytopenia: 55 vs 35%
- G3-4 infections: 31 vs 20% (pneumonias: 12 vs 4%)
- All grade ocular toxicity for BVd: 80% and 34% G3-4 (blurred vision: 66 and 22%)
- BVd arm:
  - Dose reductions: 75%; dose interruptions/delay: 94%
  - 9% of patients required to discontinue belamaf

DREAMM-8: BPd vs PVd

302 pts with ≥ 1PL (median: 1)
Len exp/ref: 100/78%; anti-CD38 exp/ref: 25/22%



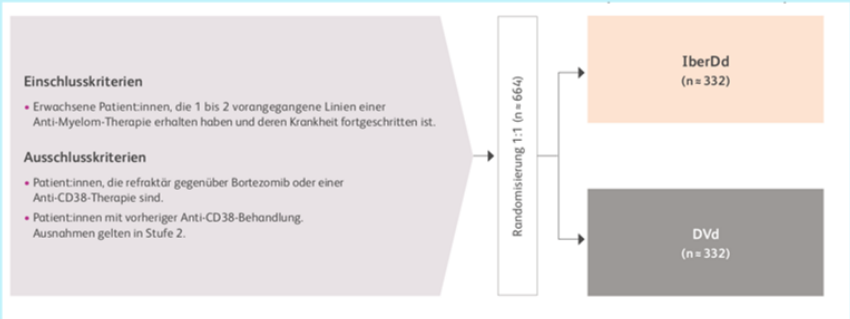
- ORR: 77% vs 72%; ≥CR rate: 40% vs 16%
- MRDng and ≥CR rate: 24% vs 5%, improved DoR, positive trend for OS (not significant, assessment ongoing)
- G3-4 thrombocytopenia: 38% vs 29%; G3-4 infections: 49% vs 26%
- All grade ocular toxicity for BPd: 89% and 43% G3-4 (blurred vision: 79 and 17%)
- BVd arm:
  - Dose reductions: 59%; dose interruptions/delay: 83%
  - 9% of patients required to discontinue belamaf

Mateos MV, et al. J Clin Oncol 2024;42(36 Suppl). Abstract 439572; Trudel MV, et al. J Clin Oncol 2024;42(17 Suppl). Abstract LBA105 + NEJM 2024

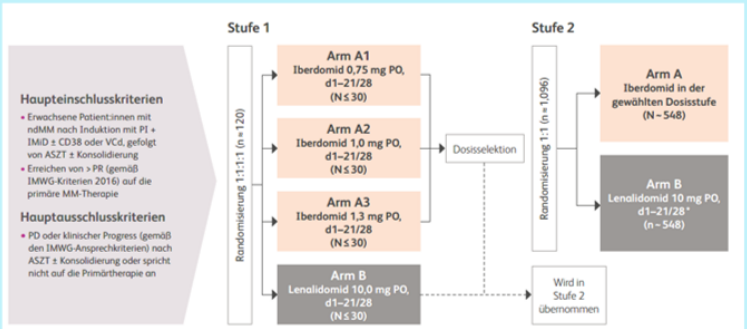
Laufende Zulassungsstudien CELMoDs

Iberdomide (CC-220)

- EXCALIBER rrMM: DVd vs. IberDd

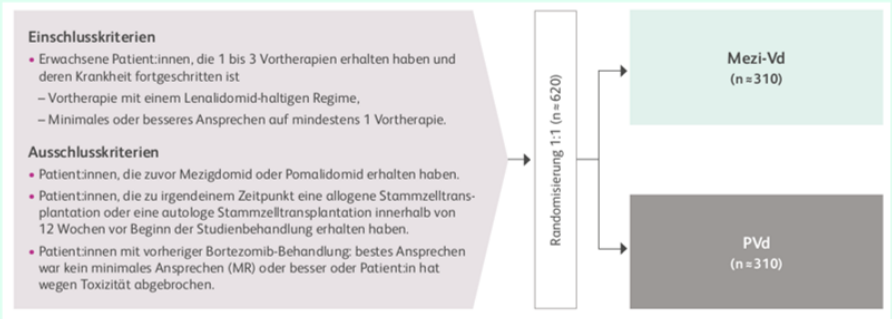


- EXCALIBER Maintenance: H2H Rev vs. Iber

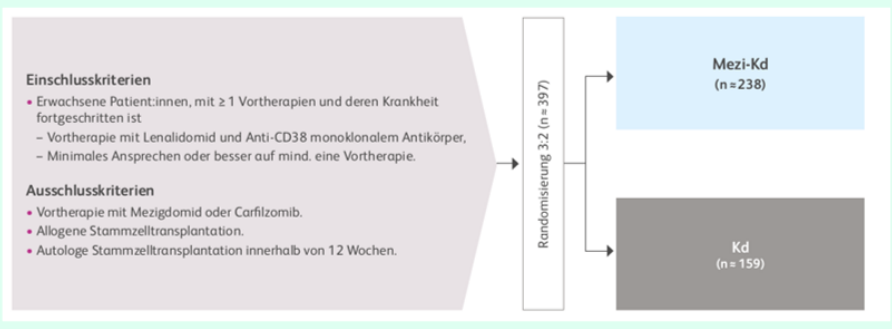


Mezigdomide (CC-92480 / CA057)

- SUCESSOR-1: MeziVd vs. PVd



- SUCCESOR-2: MeziKd vs. Kd



+ DSMMXVIII/GMMGHD9 Studie: Iberdomid vs. Isatuximab-Iberdomid als Maintenance: https://gmmg.info/gmmg-hd9-dsmm-xviii/

The mentioned agent/combinations are under investigation and have not been approved by any regulatory authority

Schlußfolgerungen

- Triple-class exposed/refractory MM-Pat. sind herausfordernd, bei denen BCMA-gerichtete Therapien, vor allem CAR-T-Zellen und bispezifische Antikörper ungeahnt tiefe + langandauernde Remissionen induzieren
- Ideale Therapiesequenz: CAR-T vor BiTEs + frühe CAR-T-Zellzentrumsvorstellung geeigneter Patienten (Zulassungsstatus war in D: nach 3 TL: PI, IMiD, CD38-exposed, keine schwere Organtoxizitäten, Therapie-motiviert -> ab sofort: nach 2 TL+TCE)
- Hohe Ansprechraten CAR-T-Zellen und langes PFS/OS -> induzieren Therapie-freie Intervalle, die bisher bei RRMM nicht möglich erschienen
- Neue Therapieoptionen beinhalten früheren CAR-T-Zelleinsatz und neue Zielantigene wie GPCR5D, Kombination von BiTEs + next generation anti-MM agents: z.b. Celmods
- CRS + ICANS sind gut behandelbar, Infektionen + Zytopenien aber frequent
- **-> Zuweiser-Zentrums-Zusammenarbeit bleibt essentiell**

Pubmed: „CARTs AND MM“: n=66 publications -> excellent Q + answers: Anderson Jr LD et al. Transplant Cell Ther 2024;30:17-37

Slide provided by the speaker based on clinical experience.