GIORNATE EMATOLOGICHE VICENTINE

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Mieloma Multiplo ricaduto: quali opzioni abbiamo, quali opzioni avremo

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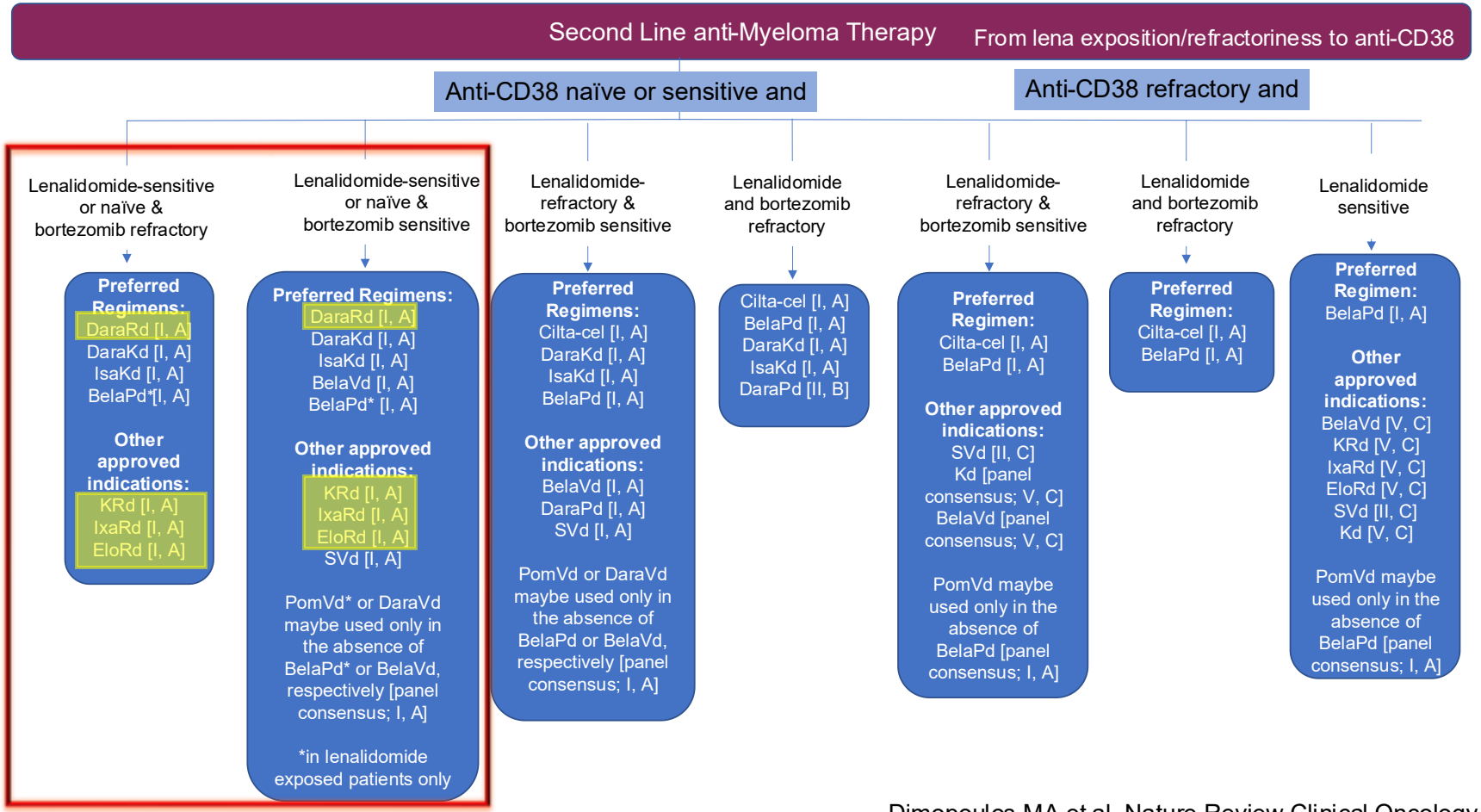
Disclosures of Katia Mancuso

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen							X
Amgen						X	X
BMS							X
Takeda	X						X
Sanofi							X
Pfizer						X	X
GSK						X	X

EHA-EMN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up



Dimopoulos MA et al, Nature Review Clinical Oncology 2025

Lenalidomide-Containing Regimens for Naïve or Lenalidomide-Sensitive Patients

EHA-EMN 2025 guidelines ⟹

Relapsed and/or refractory multiple myeloma

Patients who have received one prior line of treatment

Second-line treatment regimens are selected on the basis of the efficacy and toxicity of, and refractoriness to, the regimens received previously as well as patients' comorbidities. Patients who have not received lenalidomide or have disease sensitive to this drug should receive regimens that have been recommended in the 2021 EHA guidelines[11,12], or novel regimens supported by the data described here.

Efficacy	Carfilzomib KRd vs Rd (n=792)		Ixazomib IRd vs Rd (n=722)		Elotuzumab ERd vs Rd (n=646)		Daratumumab DRd vs Rd (n=569)	
	Tx	Control	Tx	Control	Tx	Control	Tx	Control
Median FU, mo	67.1		85		70.6		79.7	
ORR, %	87.1%	66.7%	78.3%	71.5%	79%	66%	92.9%	76.4%
CR, %	31.8%	9.3%	12%	7%	4%	7%	56.6%	23.2%
Median PFS, mo	26.1	**16.6**	20.6	**14.7**	19.4	**14.9**	45	**17.5**
PFS HR (95% CI)	0.66 (0.55-0.78) $P < .001$		0.74 (0.59-0.94) $P = .01$		0.70 (0.57-0.85) $P < .001$		0.44 0.35-0.54) $P = .0001$	
Median OS, mo	48.3	40.4	53.6	51.6	48.3	39.6	67.6	51.8
OS HR (95% CI)	0.79 (0.67-0.95) $P = .005$		0.94 (0.78-1.13) $P = .5$		0.82 (0.68-1.00) $P = .05$		0.73 (0.58-0.9) $P = .0044$	
IMiD refractory, %	21		21		–		3.5	

D, daratumumab; E, elotuzumab; FU, follow-up; ORR, overall repsonse rate; CR, complete response; PFS, progression-free survial; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152. Siegel DS, et al. *J Clin Oncol*. 2018;36(8):728-734. Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634. Richardson PG, et al. *J Clin Oncol*. 2021;39(22):2430-2442. Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631. Dimopoulous MA, et al. *Blood Cancer J*. 2020;10(9):91. Bahlis NJ, et al. *Leukemia*. 2020;34(7):1875-1884. Dimopoulous MA, et al. *J Clin Oncol*. 2023;41(8):1590-1599.

Anti-CD38–Based Regimens for Daratumumab-Sensitive Patients

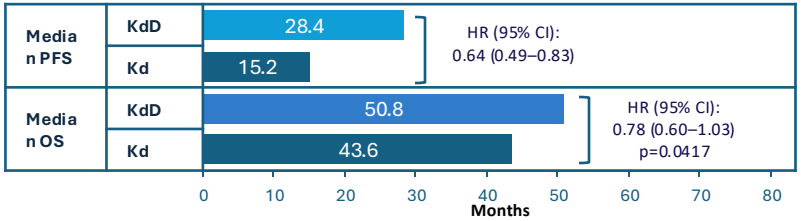
CANDOR[1]

Patients (N=466)
- ≥18 years old
- R/R MM
- 1–3 prior LOT

2:1
- KdD (n=313)
- Kd (n=154)

Primary endpoint
- PFS

Secondary endpoints
- ORR, MRD-CR at 12 mo, OS, safety



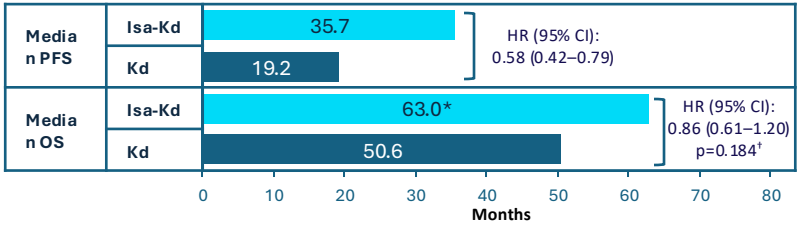
IKEMA[2,3]

R/R MM (N=302)
- 1–3 prior LOT
- No prior carfilzomib
- Not refractory to prior anti-CD38

3:2
- Isa-Kd (n=179)
- Kd (n=123)

Primary endpoint
- PFS

Secondary endpoints
- ORR, ≥VGPR with MRD-, CR rate, OS



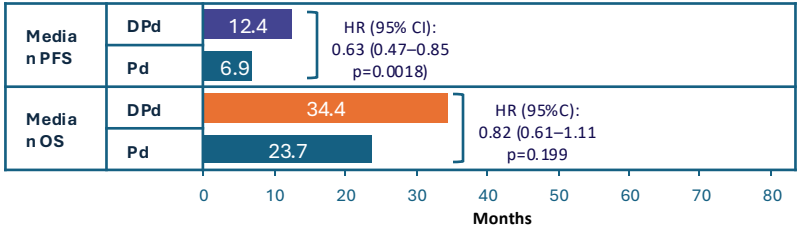
APOLLO[4]

Patients (N=304)
- R/R MM
- ≥1 prior line with both LEN and a PI
- ECOG PS ≤2
- CrCl ≥30 mL/min[2]

1:1
- DPd (n=151)
- Pd (n=153)

Primary endpoint
- PFS

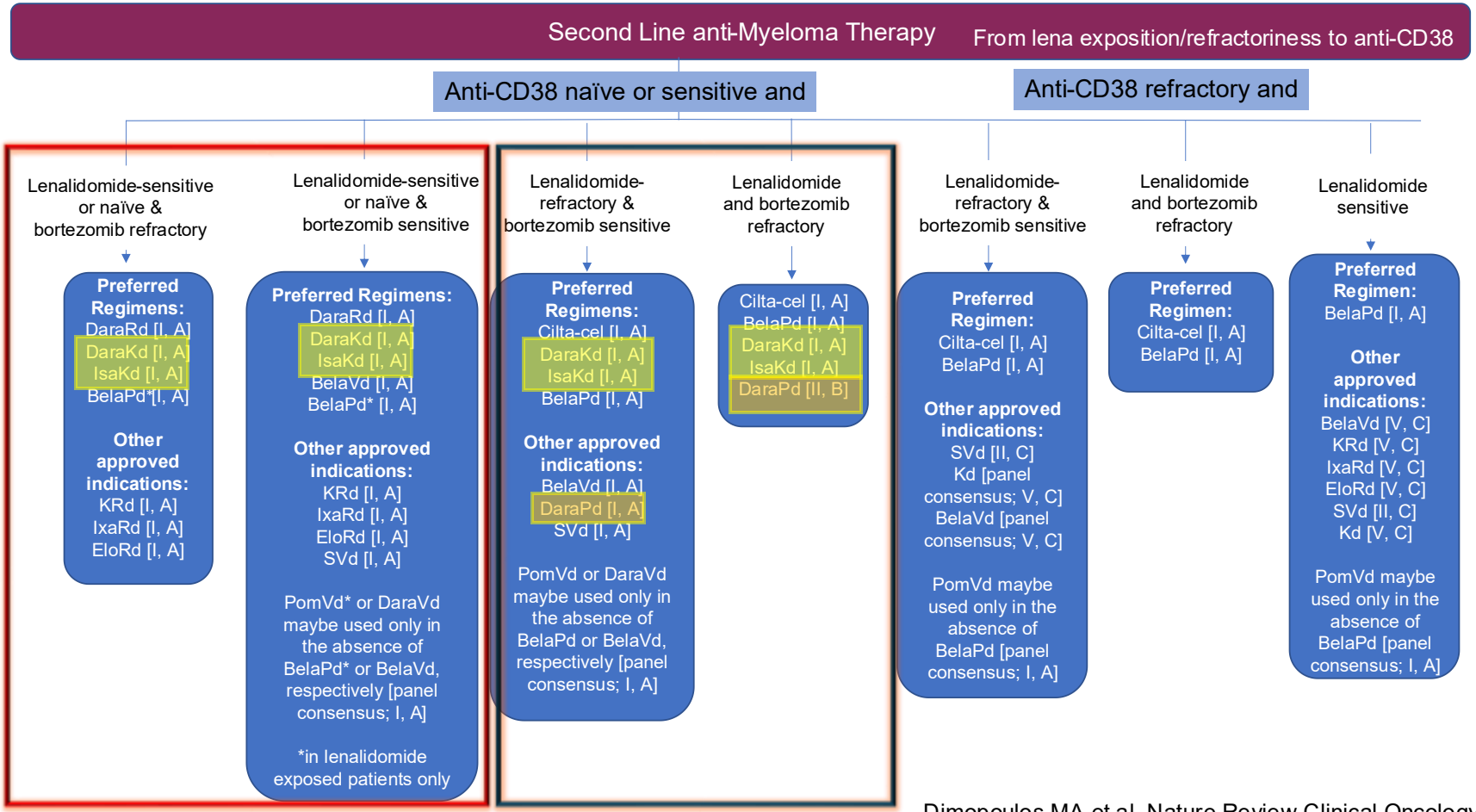
Secondary endpoints
- ORR, ≥VGPR, ≥CR, MRD, OS, time to response, DOR, TTNT, safety, HRQoL



*mOS was calculated by extrapolating the observed trend (NR [95% CI: 52.17–NR) for an additional 12 months of follow-up; this corresponds to an estimated 1-year difference in mOS; †HR correlates with difference in median OS prior to extrapolating the observed trend. CI, confidence interval; CR, complete response; CrCl, creatinine clearance; DOR, duration of response; DPd, daratumumab/pomalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; HRQoL, health-related quality of life; Isa-Kd, isatuximab/carfilzomib/dexamethasone; Kd, carfilzomib/dexamethasone; KdD, carfilzomib/ daratumumab/dexamethasone; LEN, lenalidomide; LOT, line of therapy; MM, multiple myeloma; mo, months; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; Pd, pomalidomide/dexamethasone; PFS, progression-free survival; PI, proteasome inhibitor; R/R, relapsed refractory; TTNT, time to next treatment; VGPR, very good partial response.

1. Usmani S, et al. *Blood Adv*. 2023;7(14):3739–3748; 2. Yong K, et al. *Lancet Haematol*. 2024;11(10):e741–e750; 3. Martin T, et al. *Blood Cancer J*. 2023; 13: 72; 4. Dimopoulos MA, et al. *Lancet Haematol*. 2023;10(10):e813–e824.

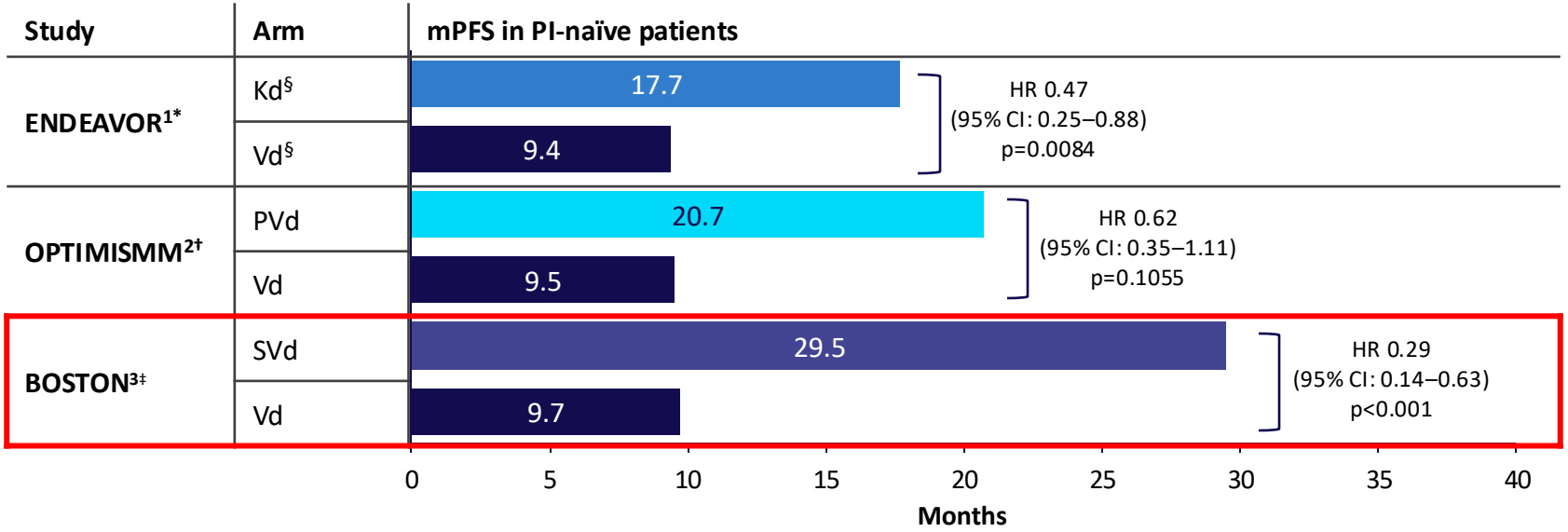
EHA-EMN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up



Dimopoulos MA et al, Nature Review Clinical Oncology 2025

Current Frontline Therapy Preserves Bortezomib Sensitivity in Most Patients

PFS in proteasome inhibitor-naïve patients



Data presented side by side for illustration purposes only – this is not a head-to-head comparison of these studies.
*Data presented are for patients without previous bortezomib treatment. Median follow-up was 11.9 months (Kd arm) and 11.1 months (Vd arm);
†After median follow-up of 15.9 months; ‡Median follow-up was 28.2 months (SVd) and 27.1 months (Vd); §intravenous administration.
CI, confidence interval; DRd, daratumumab/lenalidomide/dexamethasone; HR, hazard ratio; Kd, carfilzomib/dexamethasone; len, lenalidomide;
(m)PFS, (median) progression-free survival; (m)OS, (median) overall survival; NE, not estimable; PI, proteasome inhibitor;
PVd, pomalidomide/bortezomib/dexamethasone; SVd, selinexor/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.

1. Goldschmidt H, et al. *Leuk Lymphoma*. 2018;59(6):1364–1374; 2. Dimopoulos M, et al. *Leukemia*. 2021;35(6):1722–1731;
3. Mateos MV, et al. *Eur J Haematol*. 2024;113:242–252; 4. Kashyap T, et al. *Oncotarget*. 2016;7(48):78883–78895.

Currently licensed treatment strategies in lenalidomide-refractory MM from second line of therapy

PI-based regimens

		Overall					Len-Refractory			
Study	**Regimens**	**Prior LOTs (m)**	**mFU (mos)**	**mPFS (mos)**	**mOS (mos)**	**ORR (%)**	**Len-Ref (%)**	**mPFS (mos)**	**mOS (mos)**	**ORR (%)**
ENDEAVOR	Kd56 vs. Vd	2 (1–3)	44.3	18.7 vs. 9.4	47.8 vs. 38.8 (51.3 vs. 43.7 as 2nd LOT)	77 vs. 63	25	8.6 vs. 6.6	29.2 vs. 21.4	/
CASTOR	DVd vs. Vd	2 (1–9)	72.6	16.7 vs. 7.1 (27.0 vs. 7.9 as 2nd LOT)	49.6 vs. 38.5	84 vs. 63	24	7.8 vs. 4.9	/	/
CANDOR	DKd vs. Kd	2 (1–5)	50.6	28.4 vs. 15.2	50.8 vs. 43.6	84 vs. 73	32 vs. 36	28.1 vs. 11.1	NR vs. 38.2	79.8 (DKd)
IKEMA	isaKd vs. Kd	2 (1–4)	56.6	35.7 vs. 19.2	NR vs. 50.6	87 vs. 84	32 vs. 34	HR 0.60 in favor of isaKd	/	/
BOSTON	SVd vs. Vd	2 (1–3)	28	13.2 vs. 9.5 (21.0 vs. 10.7 as 2nd LOT)	36.7 vs. 32.8 (NR vs. 32.8 as 2nd LOT)	76 vs. 62	37 vs. 39	10.2 vs. 7.1	26.7 vs. 18.6	67.9 vs. 47.2

IMiD-based regimens

		Overall					Len-Refractory			
Study	**Regimens**	**Prior LOTs (m)**	**mFU (mos)**	**mPFS (mos)**	**mOS (mos)**	**ORR (%)**	**Len-ref (%)**	**mPFS (mos)**	**mOS (mos)**	**ORR (%)**
OPTIMISMM	PVd vs. Vd	2 (1–3)	64.5	11.7 vs. 6.9 (20.73 vs. 11.63 as 2nd LOT)	35.6 vs. 31.6	82 vs. 50	71 vs. 69	17.8 vs. 9.5 (2nd LOT)	29.8 vs. 24.2	85.9 vs. 50.8
APOLLO	DPd vs. Pd	2 (1–5)	39.6	12.4 vs. 6.9	34.4 vs. 23.7	69 vs. 46	63 vs. 73	9.9 vs. 6.5	/	/
MM-014	DPd	2 (1–2)	41.9	23.7	56.7	78.6	76	23.0	53.6	77.6

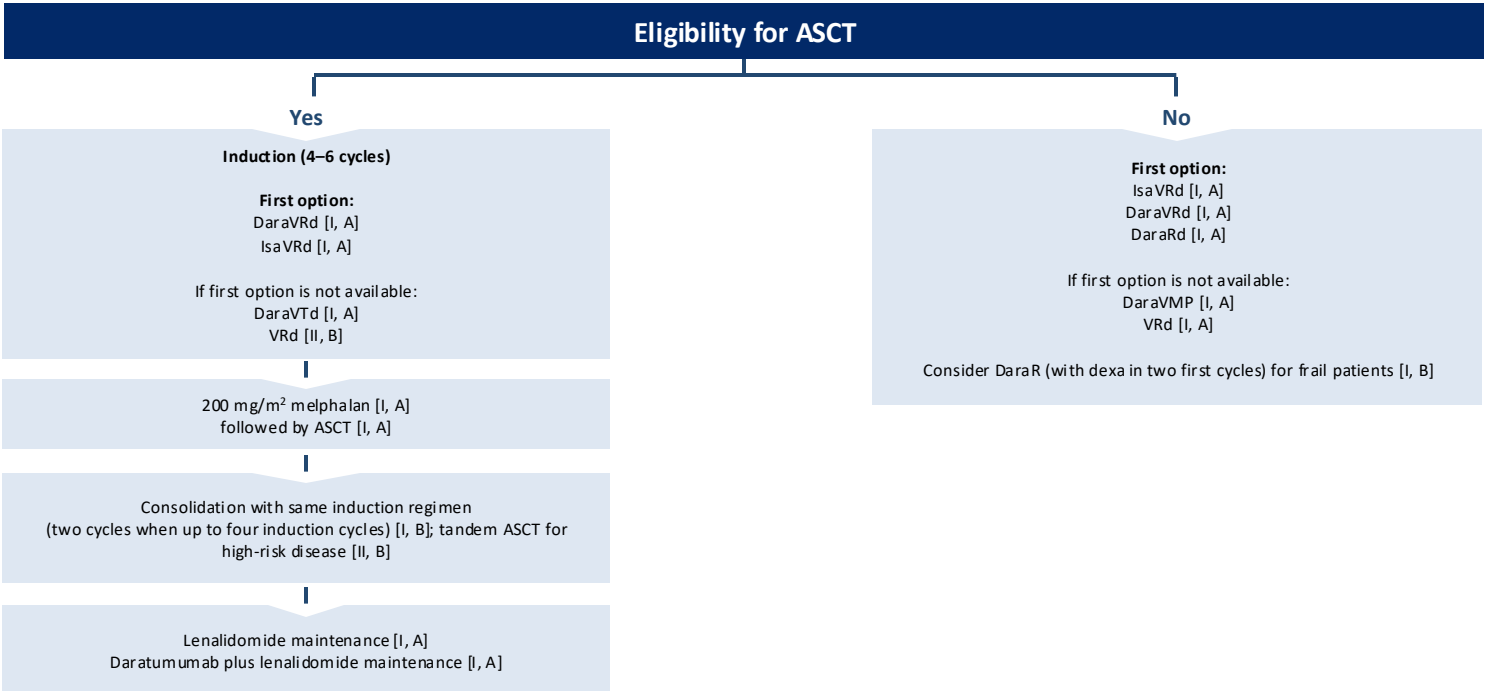
Abbreviations: DKd = daratumumab + carfilzomib + dexamethasone; DPd = daratumumab + pomalidomide + dexamethasone; DVd = daratumumab + bortezomib + dexamethasone; eloPd = elotuzumab + pomalidomide + dexamethasone; HR = hazard ratio; isaKd = isatuximab + carfilzomib + dexamethasone; isaPd = isatuximab + pomalidomide + dexamethasone; Kd = + carfilzomib + dexamethasone; Kd56 = + carfilzomib (56 mg/m²) + dexamethasone; len-ref = lenalidomide refractory patients; LOT = line(s) of therapy; m = median; mFU = median follow up; mOS = median overall survival; mPFS = median progression-free survival; mos = months; NR = not reached; ORR = overall response rate; Pd = pomalidomide + dexamethasone; PVd = pomalidomide + bortezomib + dexamethasone; Ref = references; SOC = standard of care; SVd = selinexor + bortezomib + dexamethasone; Vd = bortezomib + dexamethasone.

Mancuso K, et al. Cancers (Basel). 2025

Lenalidomide- and Anti-CD38–Containing Regimens Dominate the Frontline Setting

EHA-EMN 2025 guidelines

Recommendations for the treatment of patients with newly diagnosed multiple myeloma



- ASCT, autologous stem cell transplantation; Dara, daratumumab; dexa, dexamethasone; EHA, European Hematology Association; EMN, European Myeloma Network; Isa, isatuximab; mAb, monoclonal antibody; MM, multiple myeloma; R, lenalidomide; Rd, lenalidomide/dexamethasone; VMP, bortezomib/melphalan/prednisone; VRd, bortezomib/lenalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone.

Dimopoulos MA, Terpos E, et al. *Nat Rev Clin Oncol*. 2025

Triplets at 1L and subsequent relapses currently available in clinical practice

PIs based combinations

IsaKD
PFS: 35,7 [illegible] 0.58
CR 44%

Kd
PFS: 18.7 m, HR: 0.53
CR 13%

DaraVD
PFS: 16.7 m [illegible] 0.32
CR 30%

DaraKd
PFS: 28.6 m [illegible] 0.59
CR 29%

SVd
PFS: 13.9 HR 0.70
CR: 17%

IMiDs based combinations

DaraRd
PFS: 44.5 [illegible] .44
CR 56%

EloRd
PFS: 19.4 m [illegible] 71
CR 5%

IsaPD
PFS: 11.1m [illegible] .60
CR 10%

EloPd
PFS: 10.3m [illegible] 54
CR 8%

DaraPd
PFS: 12.4m [illegible] 63
CR 25%

IMiDs + PIs based combinations

KRd
PFS: 2[illegible] HR: 0.69
CR 32%

IxaRd
PFS: 20[illegible] HR: 0.74
CR 12%

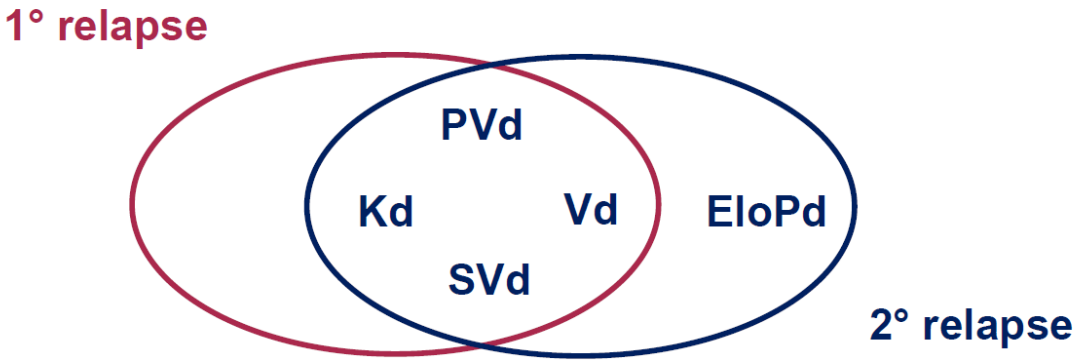
PVd
PFS: 11.2 m, HR: 0.61
CR 15%

Dimopoulos MA et al, Lancet Oncology 2016; Spencer at al, Haematologica 2018; Stewart AK et al, N Engl J Med 2015; Dimopoulos MA et al, Lancet 2020; Usmani SZ et al, Lancet Oncol 2022; Dimopoulos MA et al, Haematologica 2018; Dimopoulos MA et al, Br J Haematol 2017; Moreau P et al, NEJM 2016; Bahlis NJ et al. Leukemia 2020; Richardson PG et al, Lancet Oncol 2019; Richardson PG et al, Lacet oncol 2022; Dimopoulos MA et al, N Engl J Med 2018; Dimopoulos MA et al, ASH 2020 oral abstract

Limited «real life» treatment options for Dara-len RRMM at I relapse

On Label Regimens according to AIFA

Currently on-label available regimens



Switching target to overcome resistance

Dimopoulos et al, Ann. of Oncol. 2021

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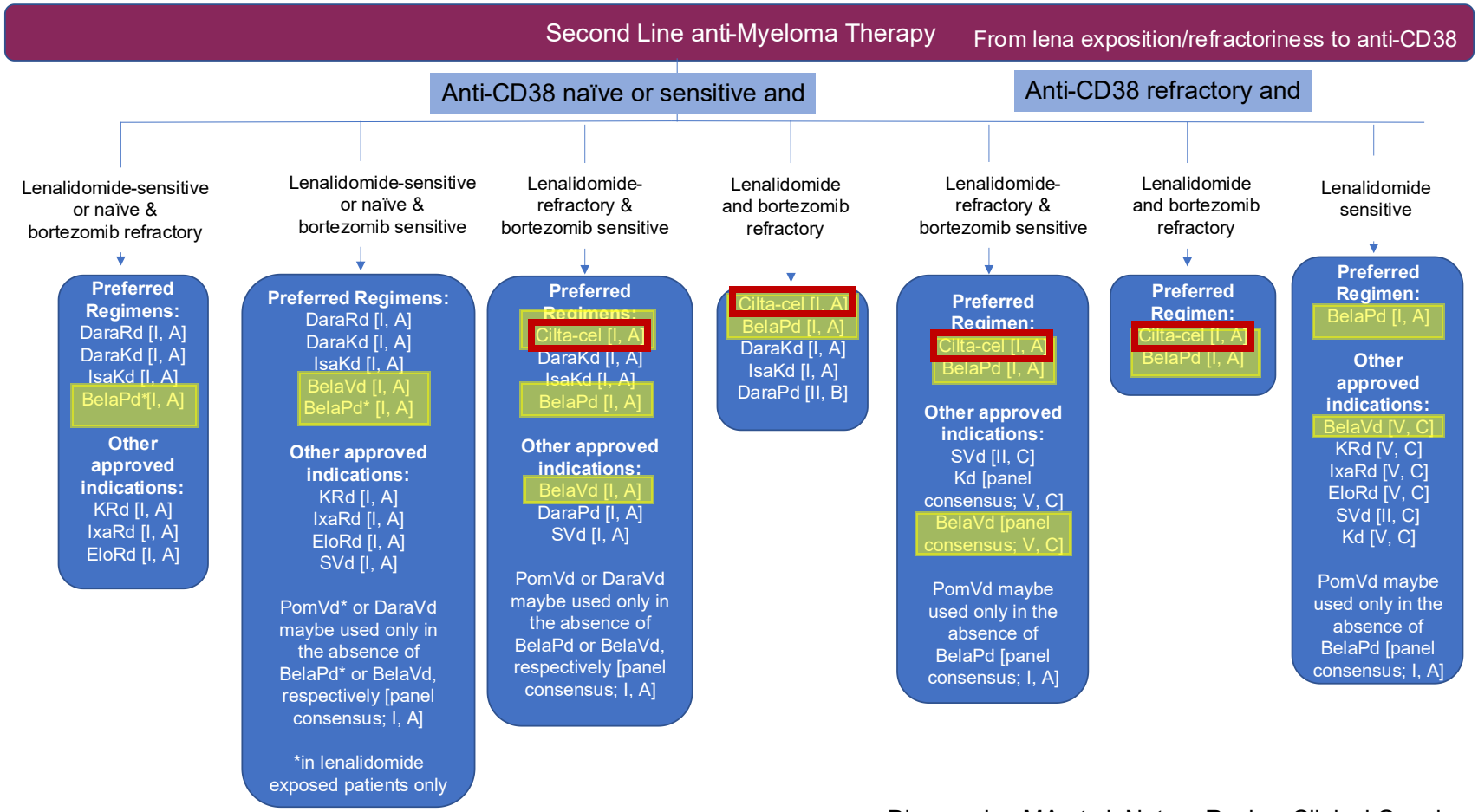
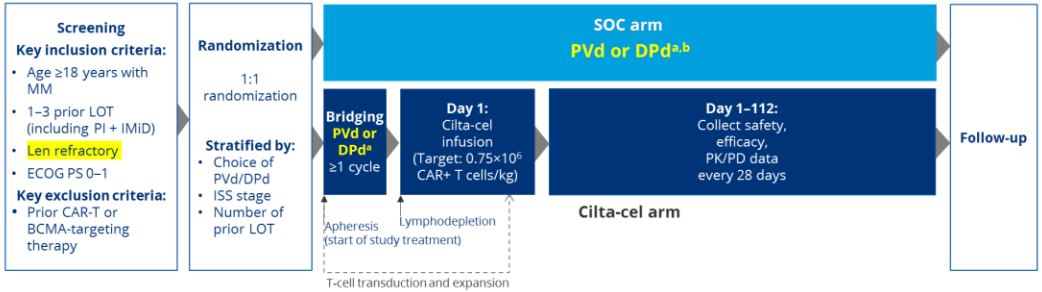


Dimopoulos MA et al, Nature Review Clinical Oncology 2025

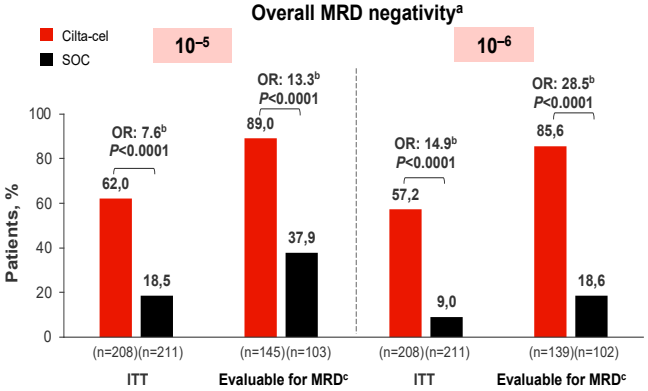
CARTITUDE-4, phase 3 trial (Len-refractory, 1-3 prior lines)



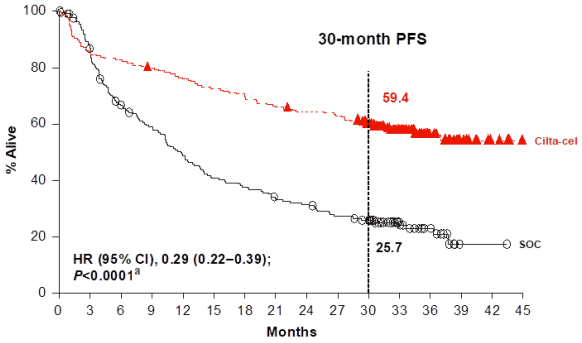
Baseline characteristic	ITT population	
	Cilta-cel (N=208)	SOC (N=211)
Age, median (range), years	61.5 (27–78)	61.0 (35–80)
Presence of soft tissue plasmacytomas,[d] n (%)	44 (21.2)	35 (16.6)
Prior LOT, median (range)	2 (1-3)	2 (1-3)
2 or more high-risk cytogenetic features	43 (20.8)	49 (23.3)
Triple-class refractory[f,h]	30 (14.4)	33 (15.6)

2 median previous regimens and 14% TCR disease

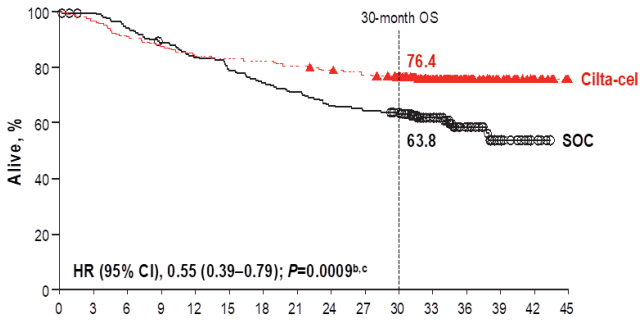
ORR 84.6%, ≥CR 76.9%



PFS (ITT; 33.6 months median follow-up)



OS (ITT; 33.6 months median follow-up)



30-month PFS and OS rates were >93% in patients with sustained (≥12 month) MRD-negative ≥CR[a]

Dhakal B et al. ASCO 2023, San Miguel J et al. N Engl Med 2023; Popat R, et al. ASH 2024 (Abstract No. 1032 – oral presentation).

Belantamab Mafodotin combos from II line: Bela-Vd and Bela-Pd

Belantamab mafodotin is an antibody–drug conjugate (ADC) that comprises an afucosylated **humanized anti-BCMA IgG1 antibody linked to the microtubule disrupting agent monomethyl auristatin F**.

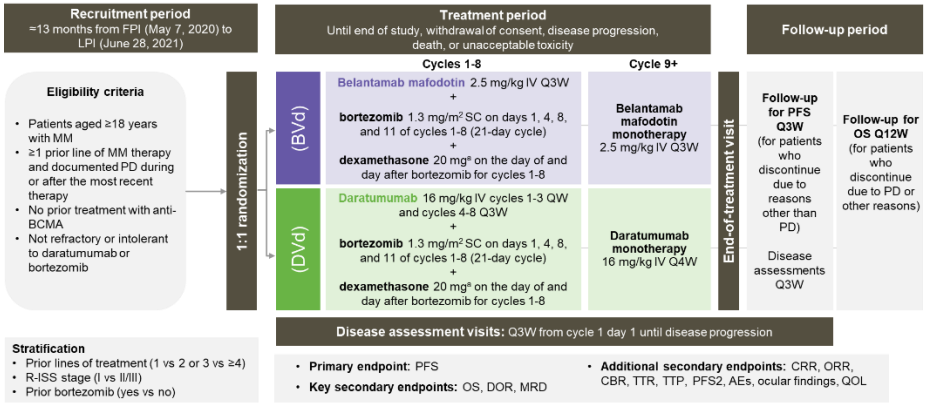
	Study design	Baseline characteristics	Median PFS, mos*	Median OS, mos*	ORR, % (95% CI)†	Safety profile‡	Belantamab-associated AEs
DREAMM-7[1]	1:1 **BVd (n=243)** vs **DVd (n=251)** **Primary endpoint:** PFS **Secondary endpoints:** OS, DOR, MRD-negative status	• **1 prior LOT**: BVd, 51%; DVd, 50% • **High-risk cytogenetics**: BVd, 28%; DVd, 27% • **LEN-refractory:** BVd, 33%; DVd, 35%	**BVd, 36.6 vs. DVd, 13.4** *HR 0.41 (95% CI: 0.31–0.53); p<0.001*	**NR vs. NR** At 18 months: **BVd, 84% vs. DVd, 73%** *HR 0.57 (95% CI: 0.40–0.80)*	**BVd, 83%** (77–87%) **vs. DVd, 71%** (65–77%)	**AEs** Any grade: 100%; Grade 3–4: 95% **Serious AEs** 50% **Discontinuation due to AEs** 26%	**Ocular events** Any grade: 79%; Grade 3–4: 34% **Blurred vision** Any grade: 66%; Grade 3–4: 22% **Worsening vision from normal to:** 20/50, 34%; 20/200, 2% **Infections** Any grade: 70%; Grade 3–4: 31%
DREAMM-8[2]	1:1 **BPd (n=155)** vs **PVd (n=147)** **Primary endpoint:** PFS **Secondary endpoints:** ORR, MRD negativity, DOR	• **1 prior LOT**: BPd, 53%; PVd, 52% • **High-risk cytogenetics**: BPd, 34%; PVd, 32% • **LEN-refractory:** BPd, 81%; PVd, 76% • **Anti-CD38 mAb-refractory:** BPd, 23%; PVd, 24%	**BPd, NR vs. PVd, 12.7** *HR 0.52 (95% CI: 0.37–0.73); p<0.001*	**NR vs. NR** 12-month estimate: **BPd, 83% vs. PVd, 76%** *HR 0.77 (95% CI: 0.53–1.14)*	**BPd, 77%** (70–84%) **vs. PVd, 72%** (64–79%)	**AEs** Any grade: 99%; Grade 3–4: 94% **Serious AEs** 63% **Discontinuation due to AEs** 15%	**Ocular events** Any grade: 89%; Grade 3–4: 43% **Blurred vision** Any grade: 79%; Grade 3–4: 17% **Worsening vision from normal to:** 20/50 34%; 20/200: 1% **Infections** Any grade: 82%; Grade 3–4: 49%

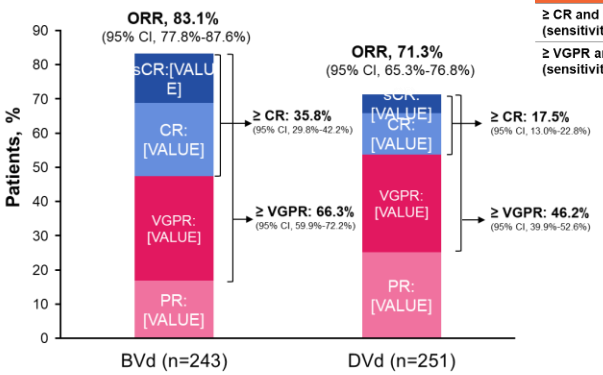
Median follow-up for DREAMM-7 was 28.2 months, and for DREAMM-8 was 21.8 months. *HRs estimated using the stratified Cox proportional hazards model and p-value was produced based on the 1-sided stratified log-rank test; †PR or better; ‡BVd arm in DREAMM-7.

AE, adverse event; BPd, belantamab mafodotin/pomalidomide/dexamethasone; BVd, belantamab mafodotin/bortezomib/dexamethasone; CI, confidence interval; DOR, duration of response; DVd, daratumumab/bortezomib/dexamethasone; HR, hazard ratio; LEN, lenalidomide; LOT, line of therapy; mAb, monoclonal antibody; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PVd, pomalidomide/bortezomib/dexamethasone.

1. Hungria V, et al. N Engl J Med. 2024;391(5):393–407; 2. Dimopoulos MA, et al. N Engl J Med. 2024;391:408–421.

DREAMM-7: BelaVd vs DaraVd

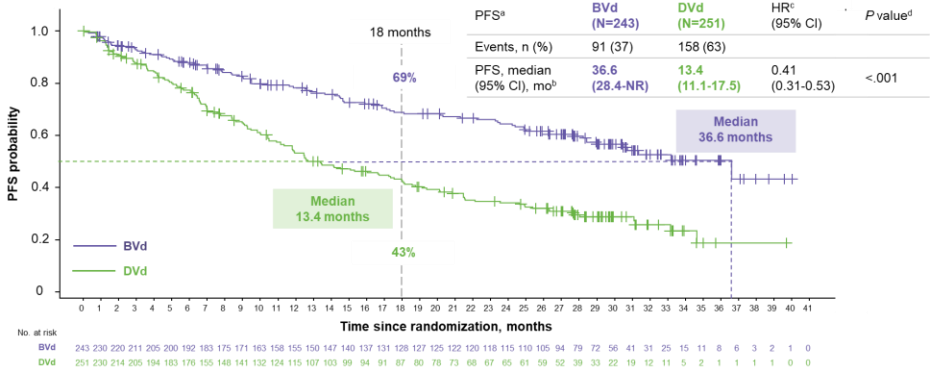




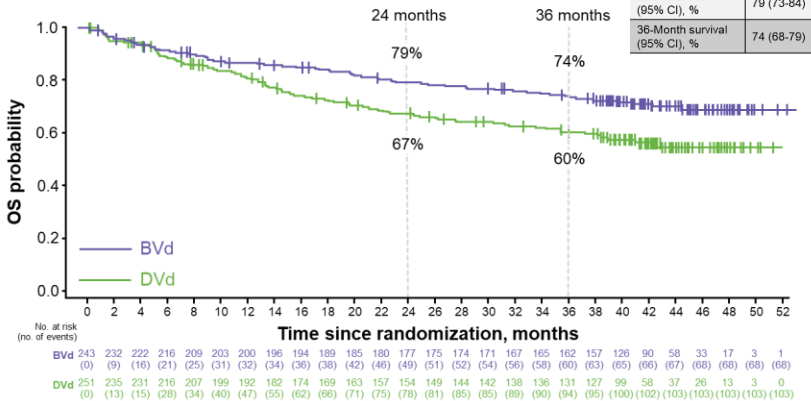
Responses (95% CI), %	BVd (N=243)	DVd (N=251)
≥ CR and MRD negativity (sensitivity of 10^{-5})[b]	25.1 (19.8-31.0)	10.4 (6.9-14.8)
≥ VGPR and MRD negativity (sensitivity of 10^{-5})[b]	38.7 (32.5-45.1)	17.9 (13.2-23.2)

Len-refractory: 33%

median follow-up of 39.4



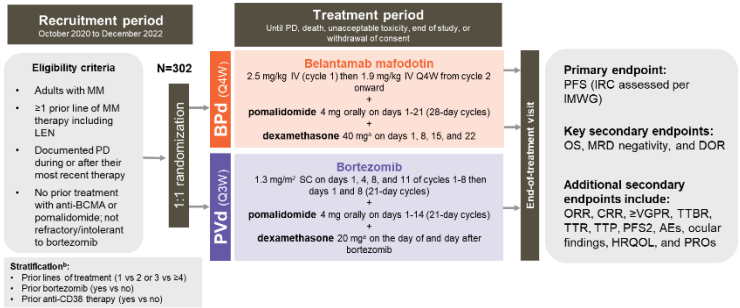
PFS[a]	BVd (N=243)	DVd (N=251)	HR[c] (95% CI)	*P* value[d]
Events, n (%)	91 (37)	158 (63)		
PFS, median (95% CI), mo[b]	36.6 (28.4-NR)	13.4 (11.1-17.5)	0.41 (0.31-0.53)	<.001

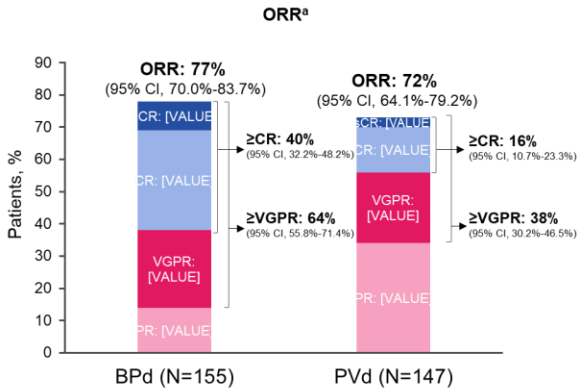


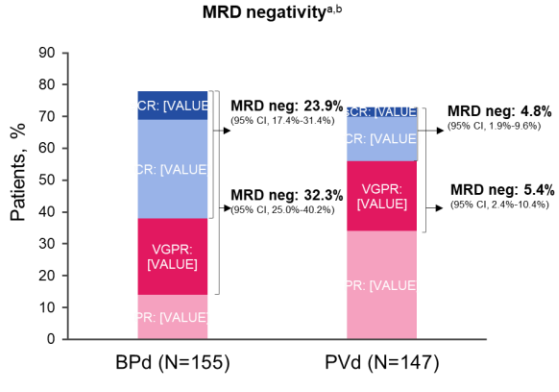
OS*	BVd (N=243)	DVd (N=251)
P value[d]	.00023	
24-Month survival (95% CI), %	79 (73-84)	67 (61-73)
36-Month survival (95% CI), %	74 (68-79)	60 (54-66)

Mateos MV et al. ASCO 2024; Hungria V et al. NEJM 2024, Hungria V et al. ASH 2024

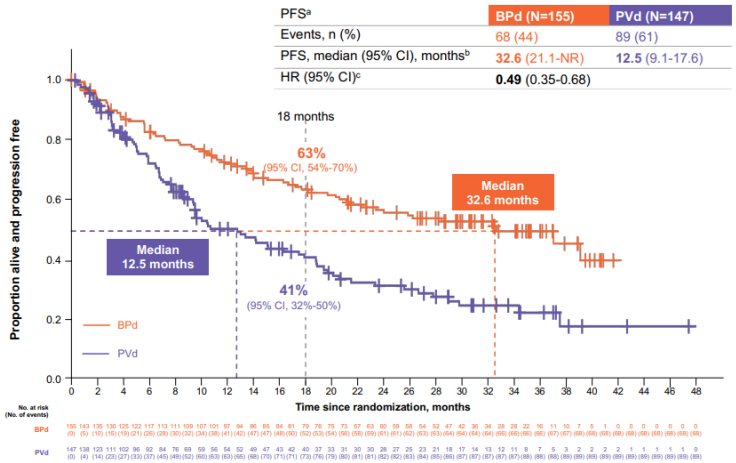
DREAMM-8: BelaPd vs PVd

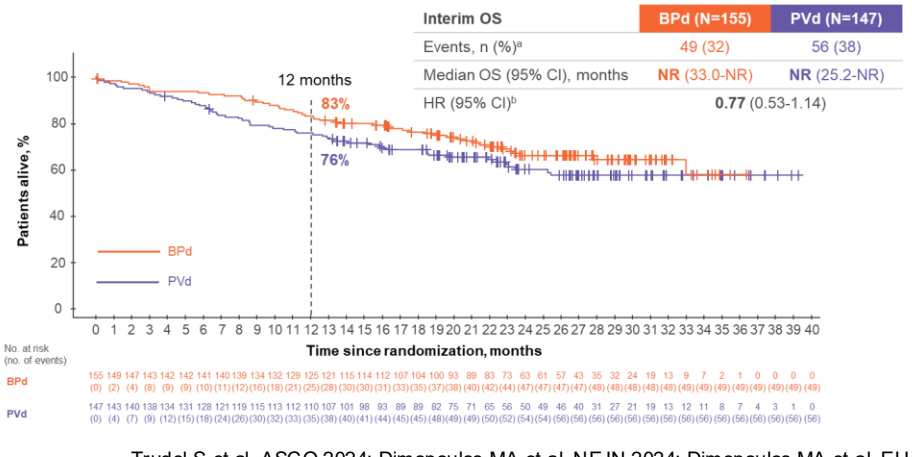






In the BPd group:
53% had received 1 prior LOT; 90% received prior PI
81% were len-refractory; **23% were anti-CD38 refractory**





Trudel S et al. ASCO 2024; Dimopoulos MA et al. NEJM 2024; Dimopoulos MA et al. EHA 2025

Clinical and patient factors: considerations for BCMA-targeted treatment options

	Belantamab mafadotin	Cilta-cel
Efficacy	**Significant PFS and OS† benefit vs SoC**[1–5]	
Safety/ tolerability	AEs experienced by almost all patients **Ocular events** can be managed and **reversed with appropriate dose modifications and follow-up**[1–3]	AEs experienced by almost all patients Black box warning for risk of **ICANS or CRS** that require **supportive care** and can be **permanent and/or fatal**[4–6]
Treatment availability	**Little to no wait** time is required prior to administration[7]	Cell manufacturing takes **~4 weeks**[8]
Administration setting	**Outpatient** (no hospitalization required)[7, 9–11]	**Specialized medical center** and/or **hospitals** Inpatient monitoring for 10 days post-infusion[6,12,13]
Monitoring	Eye exam required before first 4 doses and as clinically indicated thereafter[9–11]	Post-treatment monitoring for CRS/neurotoxicity requires patients to remain **within proximity to an administration center for ≥4 weeks** following administration[6,12,13]

*For options approved in the 2L RRMM setting; †**BPd demonstrated an early trend for OS benefit vs PVd (HR: 0.77; 95% CI: 0.53–1.14)**

#L, number of lines; AE, adverse event; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; CRS, cytokine release syndrome; d, dexamethasone; HR, hazard ratio; ICANS, immune effector cell-associated neurotoxicity syndrome; OS, overall survival; P, pomalidomide; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; SoC, standard of care; V, bortezomib.

1. Hungria V, et al. *N Engl J Med*. 2024;391:393–407; 2. Dimopoulos MA, et al. *N Engl J Med*. 2024;391:408–21; 3. Hungria V, et al. Presented at ASH, December 7–10, 2024. Oral 772; 4. Mateos MV, et al. Presented at the 21st International Myeloma Society Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil. OA–65; 5. San Miguel J, et al. *N Engl J Med*. 2023;389:335–47; 6. CARVYKTI. Prescribing Information. Janssen Biotech; 2025; 7. Herrera AF, Molina A. *Clin Lymphoma Myeloma Leuk*. 2018;18(7):452–68; 8. Barilà G, et al. *Pharmaceuticals (Basel)*. 2021;14(1):40; 9. BLENREP. Summary of Product Characteristics. GlaxoSmithKline Trading Services Limited; 2025; 10 BLENREP. Product Monograph. GlaxoSmithKline Inc.; 2025; 11. BLENREP. Summary of Product Characteristics UK. GlaxoSmithKline UK Limited; 2025; 12. CARVYKTI. Summary of Product Characteristics. Janssen-Cilag International NV; 2025; 13. CARVYKTI. Product Monograph. Janssen Inc.; 2025.

IMWG guidelines recommend referring patients early for CAR-T, and using CAR-T before ADC where both are available[1,2]

IMWG consensus recommendations for sequencing immunotherapies in MM[1]

BCMA-targeted T cell-redirecting therapies should be pursued **before BCMA-targeted ADC**, where the patient is eligible for both

Anti-BCMA CAR-T cell should be pursued **before bispecific antibodies**, where the patient is eligible for both

IMWG consensus recommendations for the referral and management of patients receiving CAR-T[2]

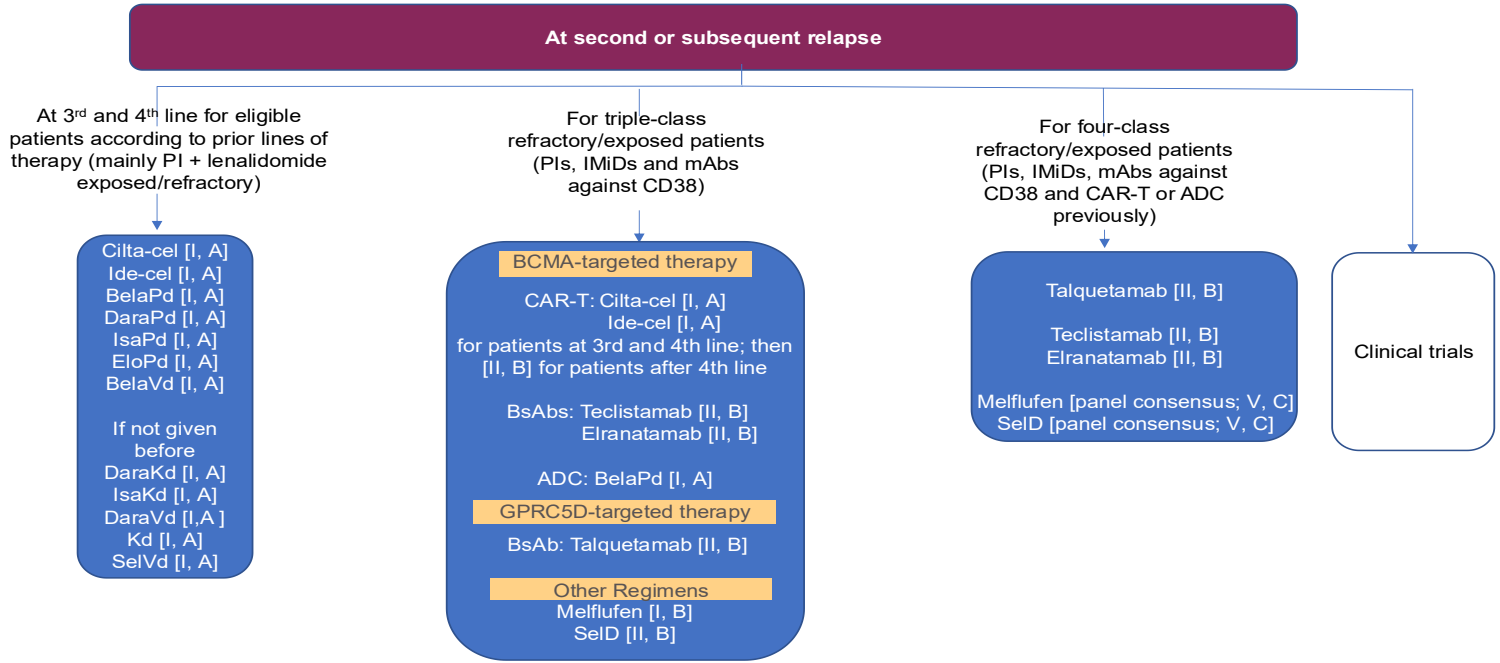
Patients should be **referred early** for CAR-T cell therapy to optimise efficacy

Cilta-cel can be used from first relapse onwards, and is the only CAR-T to be approved in this setting[3,4]

ADC, antibody-drug conjugate; BCMA, B cell maturation antigen; IMWG, International Myeloma Working Group.

1. Costa LJ, et al. Leukemia 2025;39:543–554; 2. Lin Y, et al. Lancet Oncol 2024;25:e374–e387; 3. CARVYKTI SmPC, May 2025; 4. ABECMA SmPC, November 2024.

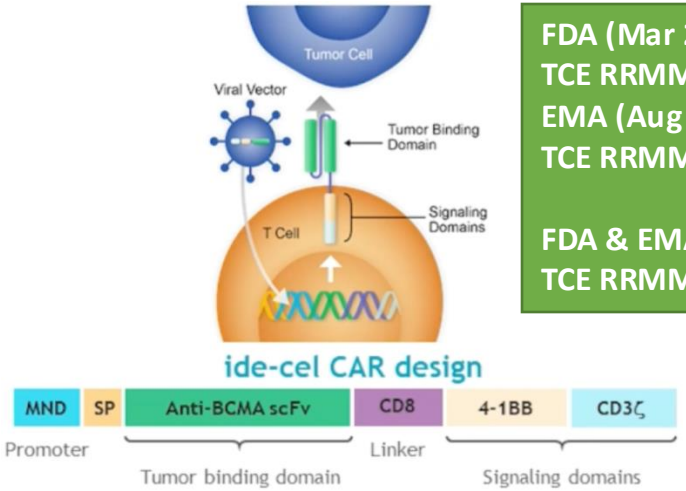
EHA-EMN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up



Dimopoulos MA et al, Nature Review Clinical Oncology 2025

Idecabtagene-Vicleucel (ide-cel)

- Autologous CAR T-cell
- **Anti-BCMA scFv**
- 4-1BB costimulatory domain
- CD3z intracellular signaling domain

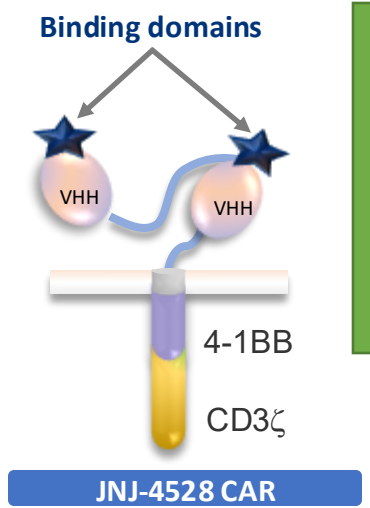


FDA (Mar 2021):
TCE RRMM, ≥ 4 prior LOT
EMA (Aug 2021):
TCE RRMM, ≥ 3 prior LOT

FDA & EMA (Apr/Mar 2024):
TCE RRMM, ≥ 2 prior LOT

Ciltacabtagene Autoleucel (cilta-cel)

- Autologous CAR T-cell
- **Two BCMA-targeting sites (to confer avidity)**
- 4-1BB signaling domain
- CD3z intracellular signaling domain



FDA (Feb 2022):
TCE RRMM, ≥ 4 prior LOT
EMA (May 2022):
TCE RRMM, ≥ 3 prior LOT

FDA & EMA (Apr 2024):
RRMM, ≥ 1 prior LOT, PI and IMiDs exposed Len-refr

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor

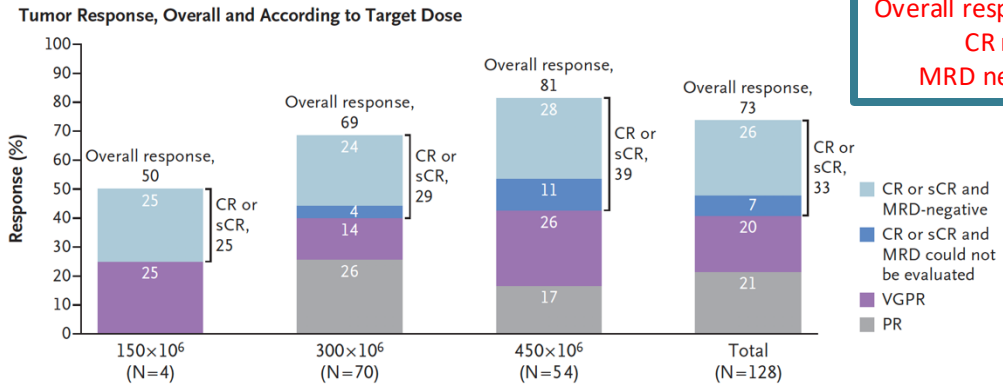
Munshi N et al. N Eng J Med 2021;384:705; Berdeja J et al. Lancet 2021;398(10297):314-24

KarMMa Phase II study of ide-cel in RRMM: key results

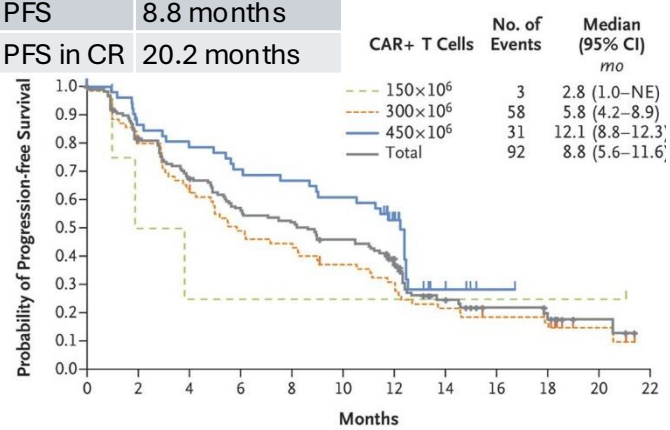
FDA/EMA Approved in 2021-AIFA approved June 2024

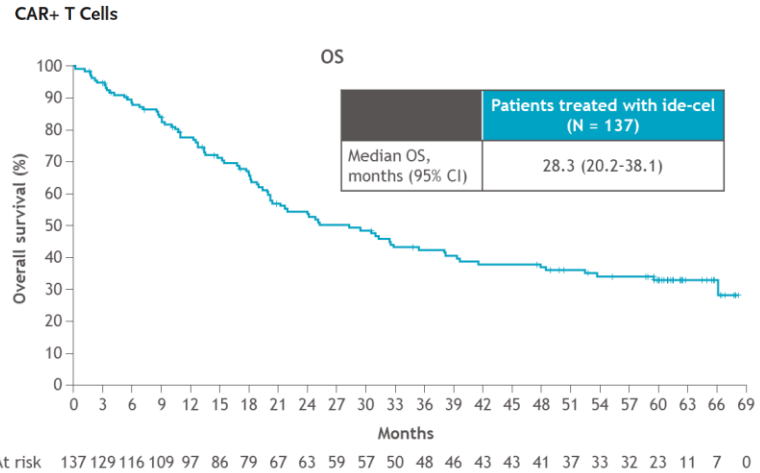
The KarMMa study evaluated the efficacy and safety of ide-cel at doses of 150–450 x 10^6 CAR+ T cells in 128 patients with RRMM after a median of 6 prior lines of therapy (84% triple refractory)[1]

Overall response rate: 73%
CR rate: 33%
MRD negativity: 26%



Survival Outcomes	
Median PFS	8.8 months
Median PFS in CR	20.2 months





Munshi NC, et al. N Engl J Med 2021;384:705-16; Anderson LD, et al. ASCO 2021 (Abstract No. 8016 – poster); Anderson LD, et al. ASH 2024.

KARMMA-3, phase 3 trial (TCE, 2-4 prior lines)

3 median previous regimes and 65% TCR disease

Key inclusion criteria

- Aged ≥ 18 years
- ECOG performance status score 0-1
- 2-4 prior regimens (including IMiD® agent, PI, and DARA)
- Refractory to the last regimen

R 2:1[a]

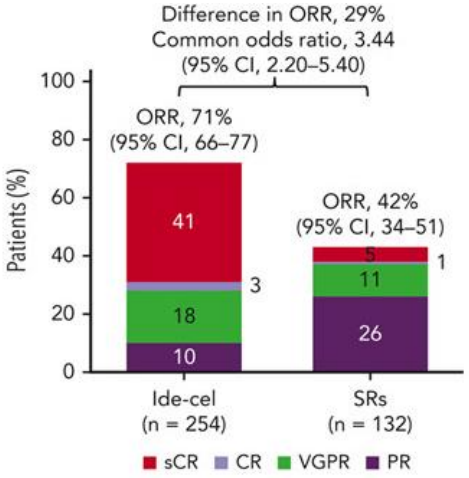
Ide-cel n = 254 → Ide-cel infusion 150-450 × 10^6 CAR+ T cells[d] n = 225

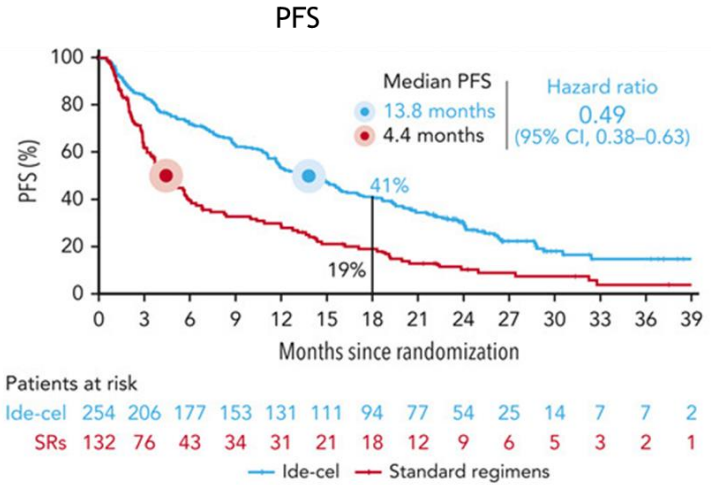
Standard regimen n = 132

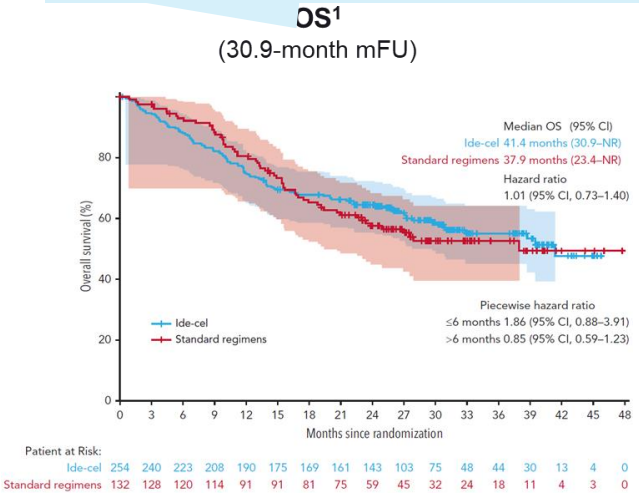
Characteristic	Ide-cel (n =254)	Standard regimens (n =132)
Median (range) age, years	63 (30-81)	63 (42-83)
Extramedullary disease, n (%)	61 (24)	32 (24)
High-risk cytogenetics, n (%)[b]	107 (42)	61 (46)
2class ref / 3class ref	169 (67) / 164 (65)	91 (69) / 89 (67)

At data cutoff, 56% of SoC patients crossed over to the ide-cel arm upon confirmed PD

Adjusting for crossover showed a trend of improved OS with ide-cel vs SoC[1] (HR, 0.72; 95% CI, 0.49–1.01)







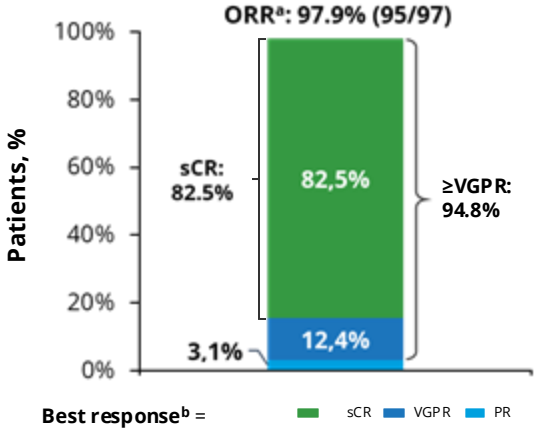
Rodriguez-Otero et al. N Engl Med 2023; . Ailawadhi S, et al. Blood 2024;144:2389-2401 (abstract); 2. Ailawadhi S, et al. Blood 2024;144:2389-2401 (visual abstract).

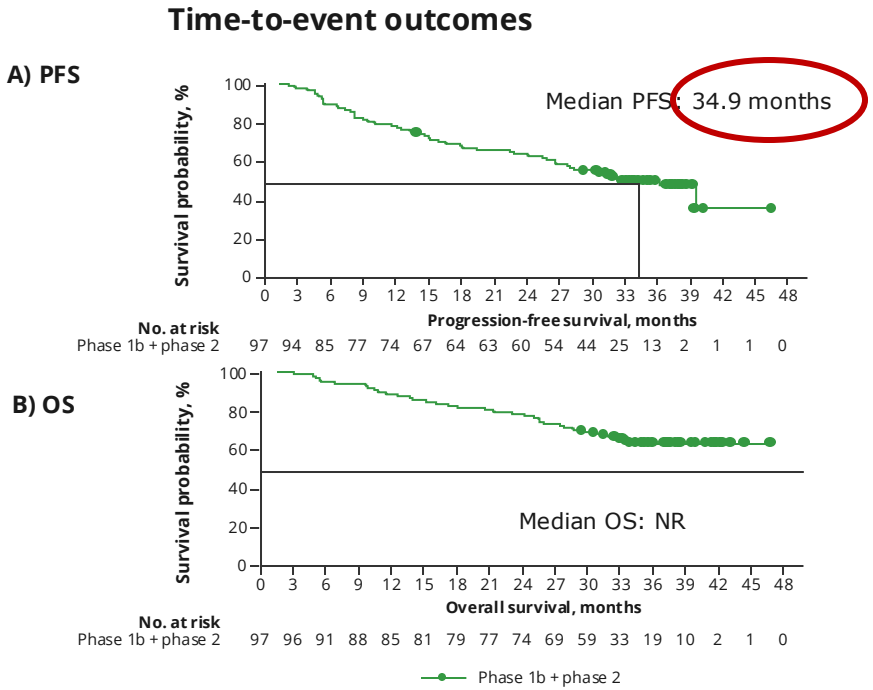
Ciltacabtagene autoleucel (Cilta-Cel)

EMA approved, AIFA pending under approval

CILTA-CEL: CARTITUDE-1 phase Ib/II trial: 6 median prior LOT

Lentiviral vector-based + 4-1BB costimulatory domain; BCMA-catching domain **targets 2 different epitopes** simultaneously

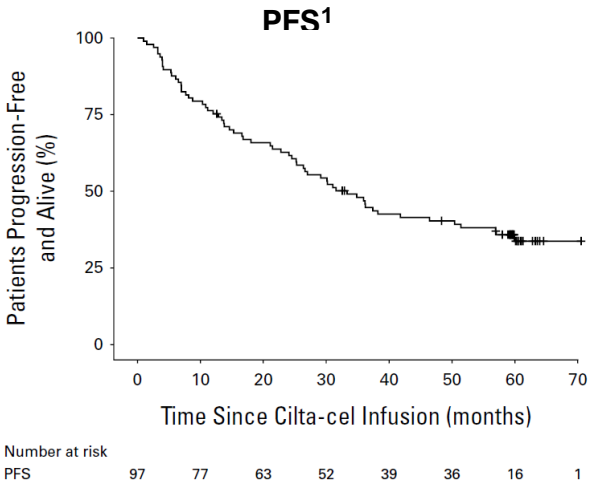


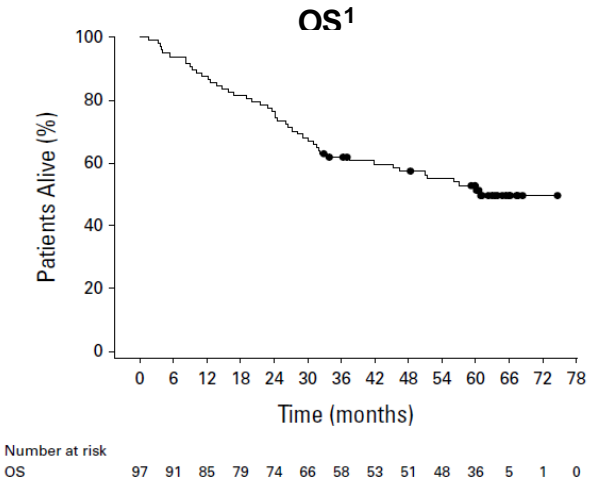


1. Madduri D, et al. ASH 2020. Presentation 177. 2. Thomas Martin et al., Oral Presentation abs. n. 549 Presented at the 63rd ASH; December 11-14, 2021; Atlanta, GA/Virtual. 3. Lin Y, et al. ASCO 2023. Poster 8009

Long-term follow-up of CARTITUDE-1 showed that 33% of patients were progression-free at >5 years with cilta-cel in TCE RRMM[1]

Overall population (N=97); mFU: 61.3 months[1]





n=32/97 (33%) patients were treatment- and progression-free at ≥5 years

mOS was **60.7 months** (95% CI, 41.9–NE)

Updated safety results[1]

In patients ≥5 years progression-free (n=32) with an additional ~28 months mFU:*

- No new cases of parkinsonism or CNP
- Two additional cases each of:
  - SPMs†
  - Neurologic events
- Four new-onset grade 3 infections

These data provide the first evidence that cilta-cel is potentially curative in patients with RRMM[1]

*Last mFU was 33.4 months. At 33.4- month mFU, no new neurotoxic events were reported since the 27.7-month mFU; a total of 26 SPMs were reported in 20 patients, of which there were 6 new cases in 4 patients at 33.4-month mFU;
†One case each of lung adenocarcinoma and anal squamous carcinoma.
CI, confidence interval; CNP, cranial nerve paralysis; EHA, EuropeanHematology Association; mFU, median follow-up; (m)OS, (median) overall survival; NE, not estimable; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; SPM, second primary malignancy.
1. Voorhees P, et al. ASCO 2025 (Abstract no. 7507 – oral presentation); Jagannath S, et al. J Clin Oncol. 2025 Sep

Approved BsAbs for RRMM

Anti-BCMA

Teclistamab

FDA (Oct 2022):
TCE RRMM, ≥ 4 prior LOT
EMA (Aug 2022):
TCE RRMM, ≥ 3 prior LOT

Registrational Trial: MajesTEC-1

Elranatamab

FDA (Aug 2023):
TCE RRMM, ≥ 4 prior LOT
EMA (Dec 2023):
TCE RRMM, ≥ 3 prior LOT

Registrational Trial: MagnetisMM-3

Linvoseltamab

CHMP EMA (Feb 2025):
TCE RRMM, ≥ 3 prior LOT

Registrational Trial: LINKER-MM1

Anti-GPRC5D

Talquetamab

FDA (Aug 2023):
TCE RRMM, ≥ 4 prior LOT
EMA (Aug 2023):
TCE RRMM, ≥ 3 prior LOT

Registrational Trial: MonumenTAL-1

Bispecific antibodies

	Teclistamab	Elranatamab	Linvoseltamab	Talquetamab
Trial	**MajesTEC-1 (NCT03145181)**	**MagnetisMM-3 (NCT04649359)**	**Linker-MM1 (NCT03761108)**	**MonumenTAL-1 (NCT03399799)**
Pts, n°	165	123	117	288 (143: 0.4 mg/kg / 145: 0.8 mg/kg)
Median age, yrs (range)	64 (33-84)	68 (36-89)	70 (37-91)	62 / 64 (46-84)
Previous LOT, median n° (range)	5 (2-14)	5 (2-22)	5 (2-16)	5 / 5 (2-14 / 2-17)
ORR, %	63	61	71	74 / 69
≥CR, %	45.5	35	52	34 / 39
Median DOR, mos	21.6	71.5% at 15 mos	29.4	9.5 / 16.9
Median PFS, mos	11.3	17.2	89% at 12 mos	7.5 / 11.2
Median OS, mos	21.9	21.9	31.4	76% / 77% at 12 mos
CRS (G ≥3), %	72 (<1)	58 (0)	46 (1)	77 / 74 (2 / 1)
ICANS (G ≥3), %	3 (0)	3 (0)	8 (2.6)	11 / 10 (1.4 / 1.4)
G ≥3 anemia, %	38	37	31	31 / 26
G ≥3 neutropenia, %	65.5	49	42	30 / 22
G ≥3 thrombocytopenia, %	22	24	14.5	20 / 18
Infections (G ≥3), %	80 (55)	70 (46)	74 (33)	59 / 68 (20 / 19)
Other relevant TEAEs (G ≥3), %	/	/	/	Skin-related events:56 / 73 (<1)
				Nail-related events:54.5 / 54 (0)
				Dysgeusia: 72 / 71 (NA)

1. Van de Donk NWCJ, et al. ASCO 2023 (Abstract No. 8011 – presentation); 2. . Lesokhin AM, et al. Nat Med 2023; doi: 10.1038/s41591-023-02528-9. Online ahead of print; 3. Chari A, et al. N Engl J Med 2022;387:2232-2244; 4. Schinke CD, et al. ASCO 2023 (Abstract No. 8036 – oral presentation); 5. Chari A, et al. ASH 2022 (Abstract No. 157 – presentation); 6. Bumma M, et al. JCO 2024; 7. Shah MR, et al. ASH 2024

Future Therapies in RRMM

1. Bispecific Antibodies

- In combination with other agents (IMiDs, anti-CD38…)
- Dual bispecifics (RedirecTT-1 trial: Talquetamab + Teclistamab in RRMM patients with EMD)
- Trispecifics (JNJ-5322 Trispecific targeting CD3, BCMA, and GPRC5D)

2.CAR-T Cells

- Novel constructs targeting BCMA
- Novel targets beyond BCMA, including GPRC5D (Arlo-cel)

3. CELMoDs (Iberdomide and Mezigdomide)

- Next-generation cereblon E3 ligase modulators
- Enhanced immunomodulatory activity

Future Directions

BCMA-targeting BsAbs are also being investigated in earlier lines: Phase III studies

Study	Treatment line	Treatment arms
MajesTEC-3[1]	1-3 prior LOT	Teclistamab + Dara, Dara-Pd or Dara-Vd (comparator)
MajesTEC-4[2]	TE NDMM	Teclistamab + R, Teclistamab, R (comparator)
MajesTEC-7[3]	TIE* NDMM	Teclistamab + Dara-R, talquetamab + Dara-R, Dara-Rd (comparator)
MajesTEC-9[4]	1-3 prior LOT	Teclistamab, PVd or Kd (comparator)
MagnetisMM-5[5]	>1 prior LOT	Part 2: Elranatamab, elranatamab + Dara, Dara-Pd (comparator)
MagnetisMM-6[6]	TIE NDMM	Part 2: Elranatamab + Dara-R, Dara-Rd (comparator)
MagnetisMM-7[7]	TE NDMM	Elranatamab, lenalidomide (comparator)
MagnetisMM-32[8]	1-4 prior LOT	Elranatamab, Elo-Pd or PVd or Kd (comparator)
MonumenTAL-6[9]	1-4 prior LOT	Talquetamab + pomalidomide, talquetamab + teclistamab, elotuzumab + Pd or PVd (comparator)

Daratumumab depletion of CD38-expressing Tregs may potentiate teclistamab/talquetamab-mediated killing of myeloma cells

*Not eligible or not intended for transplant. ASCT, autologous stem cell transplantation; Dara, daratumumab; DRd, daratumumab-lenalidomide-dexamethasone; DPd, daratumumab-pomalidomide-dexamethasone; DVd, daratumumab-bortezomib-dexamethasone; EPd, elotuzumab-pomalidomide-dexamethasone; IMiD, immunomodulatory drug; Kd, carfilzomib-dexamethasone; LOT, lines of therapy; PVd, pomalidomide-bortezomib-dexamethasone; RRMM, relapsed/refractory multiple myeloma; SVd, selinexor-bortezomib-dexamethasone. 1. NCT05083169; 2. NCT05243797; 3. NCT05552222; 4. NCT05572515; 5. NCT05020236; 6. NCT05623020; 7. NCT05317416; 8. NCT06152575; 9. NCT06208150. All clinical trial pages accessed at: https://clinicaltrials.gov/ (last accessed June 2024).

Future Directions

RedirecTT-1
Phase 2 Study of Talquetamab + Teclistamab in Patients With RRMM and EMD

Key eligibility criteria

EMD defined as:
≥1 nonradiated bone-independent soft tissue plasmacytoma ≥2 cm in greatest dimension confirmed by central review of PET-CT scans[a,b]

- MM per IMWG criteria
- Triple-class exposed[c] RRMM
- Prior CAR-T (≤20% patients) and BsAb therapy permitted
  - BsAbs could not target GPRC5D or BCMA
- Nonsecretory/oligosecretory disease permitted

Step up doses[d] administered 2–4 days apart

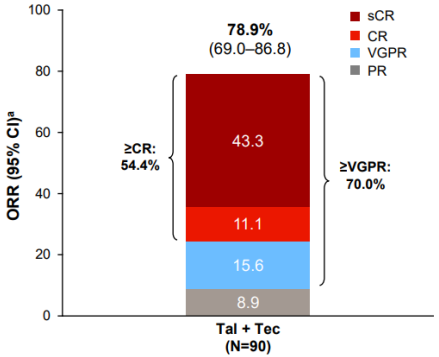
- Tal 0.4 mg/kg Tec 1.5 mg/kg
- Tal 0.06 mg/kg Tec 0.3 mg/kg
- Tal 0.01 mg/kg Tec 0.06 mg/kg

Tal 0.8 mg/kg Q2W SC + Tec 3.0 mg/kg Q2W SC[d] until disease progression

Primary endpoint
- ORR[e] (EMD response assessed by central radiology review of whole-body PET-CT scans)

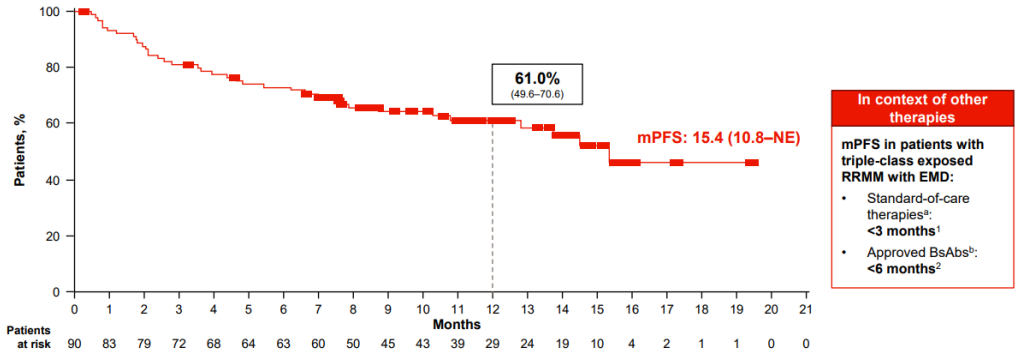
Secondary endpoints
- ≥VGPR, ≥CR, and sCR rate[e]
- Time to response,[e] DOR,[e] PFS, and OS
- Safety
- PK, immunogenicity

Option to reduce dosing frequency for both agents to monthly dosing after:
- ≥VGPR and minimum 4 cycles of therapy, *or*
- 6 cycles, per investigator discretion



Parameter	Tal + Tec (N=90)
Median (range) follow-up, months	12.6 (0.5–19.5)
Median (range) time to first response, months	2.6 (1.0–5.8)
Median (range) time to best response, months	4.7 (1.0–11.9)

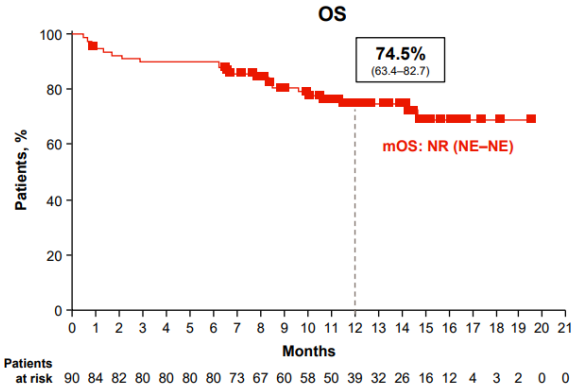
Prior therapy	ORR	95% CI
Anti-BCMA CAR-T, % (n/N)	83.3 (15/18)	58.6–96.4
Anti-FcRH5 BsAb, % (n/N)	75.0 (6/8)	34.9–96.8
Belantamab mafodotin, % (n/N)	90.9 (10/11)	58.7–99.8



In context of other therapies

mPFS in patients with triple-class exposed RRMM with EMD:
- Standard-of-care therapies[a]: **<3 months**[1]
- Approved BsAbs[b]: **<6 months**[2]

Estimated PFS rate at 1 year was 61%



Estimated 12-month OS rate was 75%

Kumar S et al. EHA 2025

Future Therapies in RRMM

1. Bispecific Antibodies

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- Dual bispecifics (RedirecTT-1 trial: Talquetamab + Teclistamab in RRMM patients with EMD)
- Trispecifics (JNJ-5322 Trispecific targeting CD3, BCMA, and GPRC5D)

2.CAR-T Cells

- Novel constructs targeting BCMA
- Novel targets beyond BCMA, including GPRC5D (Arlo-cel)

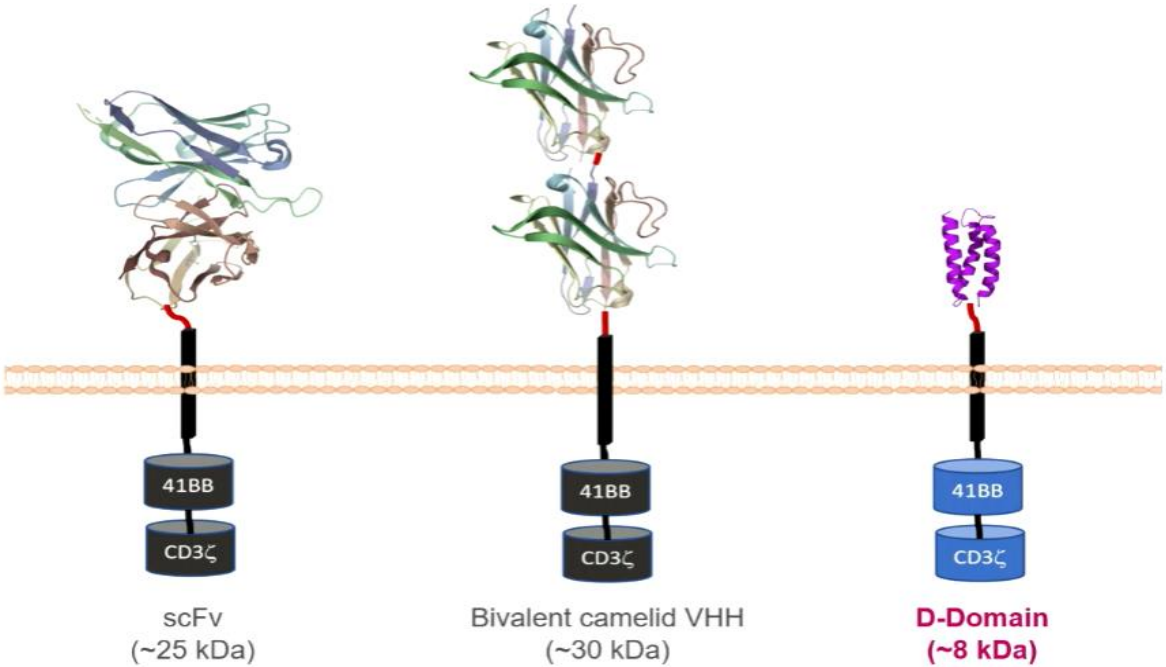
3. CELMoDs (Iberdomide e Mezigdomide)

- Next-generation cereblon E3 ligase modulators
- Enhanced immunomodulatory activity

Future Directions

Anitocabtagene autoleucel (anito-cel/CART-ddBCMA)

Autologous BCMA-directed CAR T-cell therapy using a novel, D-Domain binder[1,2]



scFv (~25 kDa)

Bivalent camelid VHH (~30 kDa)

D-Domain (~8 kDa)

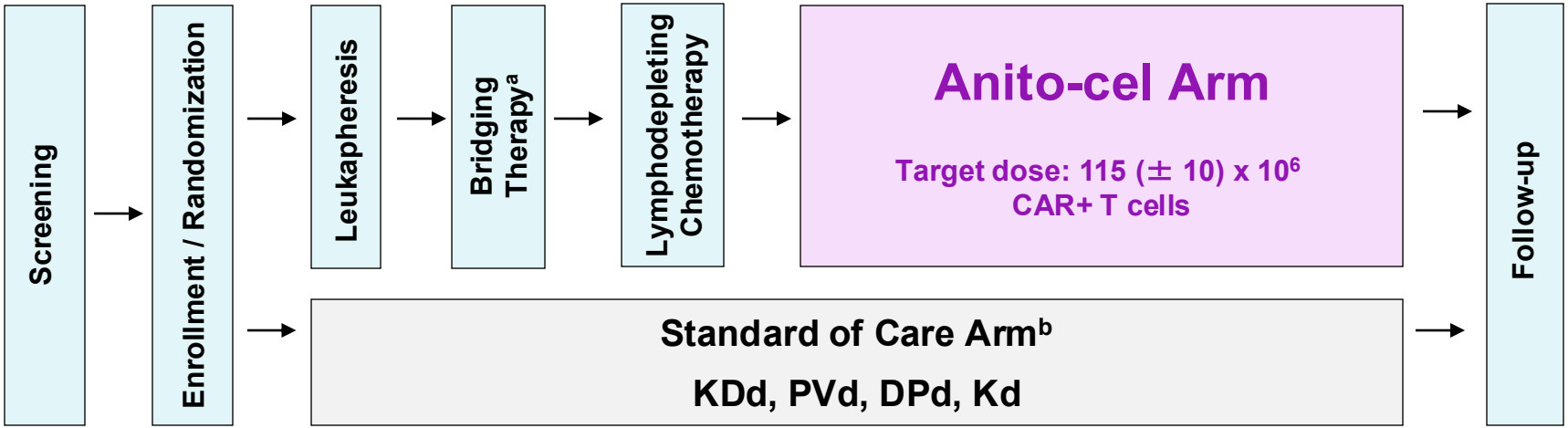
D-Domain Attributes:
Non-Antibody Derived Synthetic Protein[1,2]

Size	**Small D-Domain construct facilitates high transduction efficiency and CAR positivity[2-4] resulting in a low total cell dose**
Structure & Stability	**D-Domain CARs are stable and lack tonic signaling[4,6] due to the rapid folding, lack of disulfide bonds, and hydrophobic core[5,6] of the D-Domain**
Binding	**The D-Domain binder has a fast off-rate[4] and high CAR surface expression[4]. This combination may allow optimal tumor cell killing without prolonged inflammation**

[1]Rotte, et al. Immuno-Oncology Insights 2022; 3(1), 13–24. [2]Frigault, et al. Blood Adv. 2023; 7(5) 768-777. [3]Cante-Barrett, et al. BMC Res. Notes 2016; 9:13. [4]Buonato, et al. Mol. Cancer Ther. 2022; 21(7) 1171-1183. [5]Zhu, et al. Proc. Nat. Acad. Sci. 2003; 100(26): 15486-15491; [6]Qin, et al. Mol. Ther. 2019; 27(7): 1262-1274.

Phase 3 randomized iMMagine-3 trial: ANITO-CEL vs SOC in triple-class exposed patients

1-3 prior LoT, including a PI, an anti-CD38 monoclonal antibody and an iMiD



STUDY DESIGN

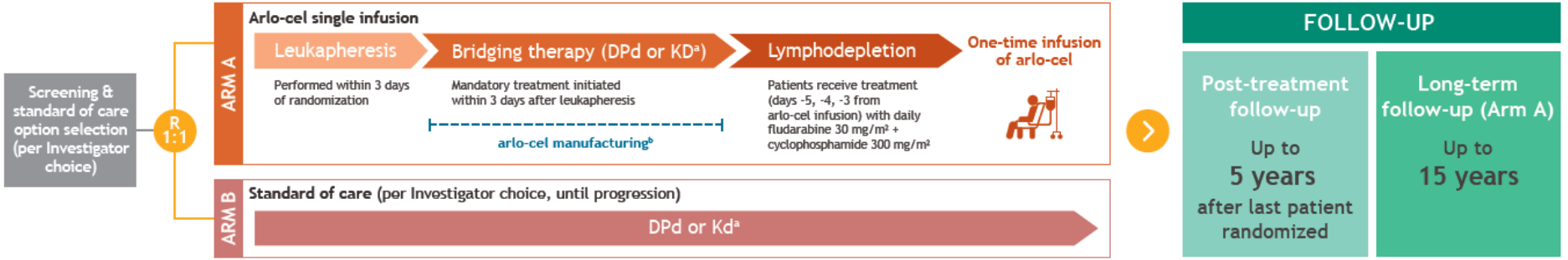
- 1:1 Randomization
- n = Approximately 450, ~130 sites globally

STUDY ENDPOINTS

- Primary Endpoint: PFS
- Key Secondary Endpoints: CR rate, MRD, OS, safety

[a] Optional Bridging therapy will be the SOC regimen selected prior to randomization
[b] Cycles will continue until unacceptable toxicity, progression as per IMWG criteria, or patient withdrawal of consent

QUINTESSENTIAL-2 a phase 3 study of arlo-cel versus standard of care in RRMM patients (refractory to lenalidomide)



DUAL PRIMARY ENDPOINTS

- Progression-free survival (PFS)[a]
- Minimal residual disease (MRD) negativity in complete response (CR)[b]

SECONDARY ENDPOINTS

KEY

- Overall survival (OS)
- Overall response rate (ORR)[a]

OTHER

- Safety and tolerability[c]
- CR rate[a]
- Time to response (TTR)[a,d]
- Duration of response (DOR)[e]
- MRD-negative status
- Pharmacokinetics
- Patient-reported quality of life outcomes (EORTC QLQ-C30 and -MY20)

Key Eligibility Criteria

INCLUSION CRITERIA

- Men and women ≥18 years of age
- Documented diagnosis of MM per IMWG criteria
- Received 1-3 prior LOT[a] and refractory to lenalidomide as per IMWG guidelines (progression on or within 60 days of completing lenalidomide therapy)
- Measurable disease during screening
- ECOG performance status 0 or 1
- Documented disease progression during or after their last anti-myeloma regimen

EXCLUSION CRITERIA

- Active or history of central nervous system involvement with MM
- Solitary plasmacytomas or non-secretory myeloma without other evidence of measurable disease
- Need for urgent treatment due to rapidly progressing MM
- Active systemic fungal, bacterial, viral, or other infection despite appropriate anti-infective treatment at time of leukapheresis
- Received any prior GPRC5D-directed therapy or other prior MM treatment without the required washout prior to leukapheresis

Planned enrollment

QUINTESSENTIAL-2

- **Study start date (first patient first visit):** March 12, 2025
- **Estimated primary analysis completion date:** December 30, 2027
- **Estimated study completion date:** July 21, 2032
- **Estimated enrollment:** 440

CONCLUSIONS

• Over the past two decades, **therapeutic advances** have profoundly changed the natural history of MM, with a potential for a curable patient fraction.

• A relevant unmet clinical need remains for patients refractory to lenalidomide and anti-CD38 antibodies as early as the second line.

• **Novel immunotherapies** (ADC, CAR-T and TCE) are reshaping the **standard of care** from the second line of therapy.

• In RRMM, **several effective options are available**, but **multi-class refractoriness may arise** after only a few treatment lines, making the “per-line” approach less suitable for regulatory purposes.

•**Optimal sequencing** of therapies has become **a key goal** in patients management.

THANK YOU FOR THE ATTENTION

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