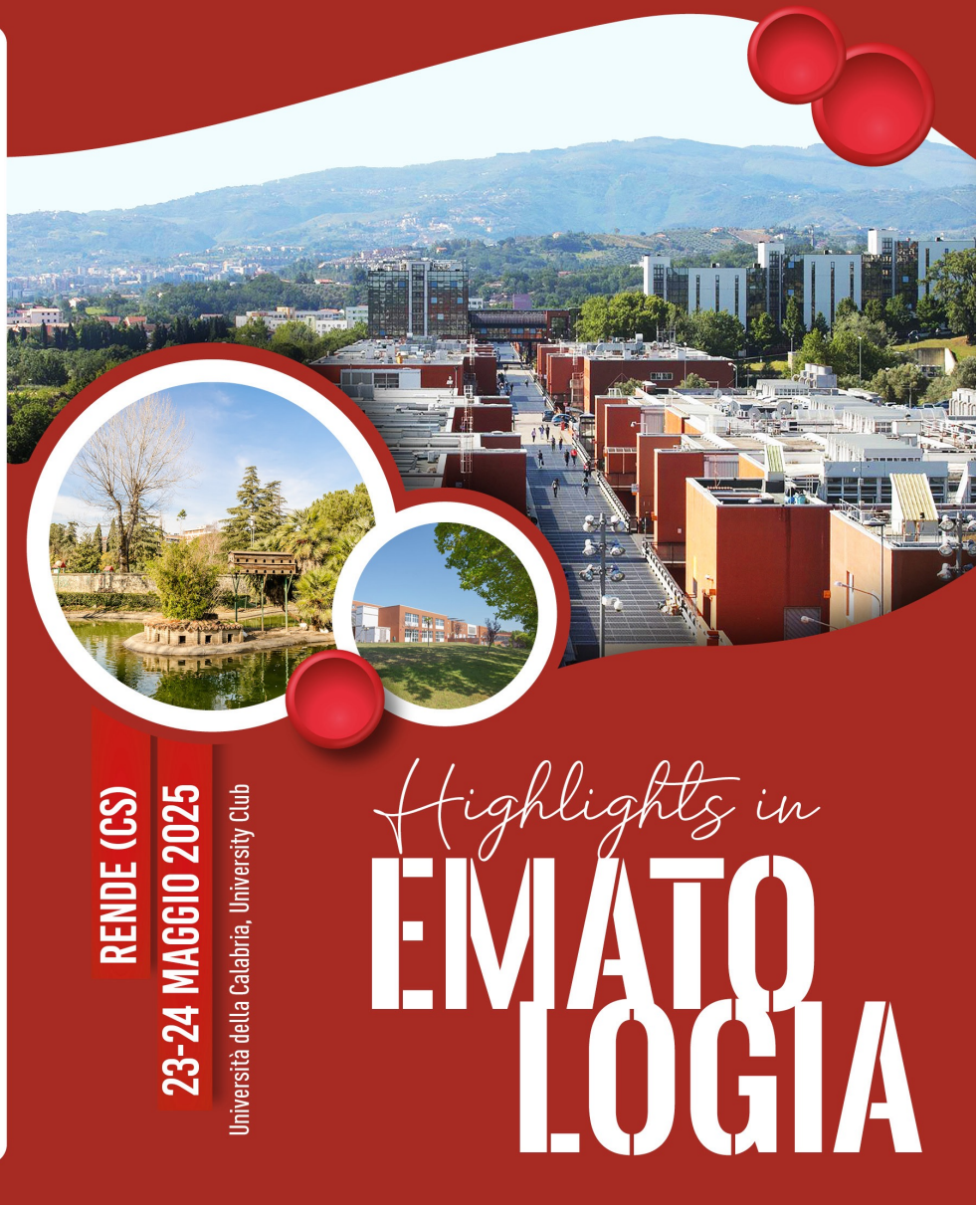
CASO CLINICO
MIELOMA

E.A. Martino
UOC Ematologia
Cosenza



CASE REPORT V.D.: M, 57 years

Onset → 2019: incidental finding of paraprotein in W&W
2020: increased level of paraprotein (7 gr/dl) and anemia

Blood tests (2020) → : Hb 9,7 gr/dl, creat 0,8 mg/dl (eGFR > 60 ml/min), calcium 9,4 mg/dl, B2M 4,2 mh/dl, sIFE positive for IgGk, physiological 24 h proteinuria

18F-FDG PET/TC (2020) → lytic lesions (pelvis, iliac wings, D11)

Bone marrow (2020) → PC 80%; FISH positive for (4;14)

MM IgGk, ISS 2, R-ISS 2
Treatment criteria: PC 80%
bone disease
anemia

CASE REPORT V.D.: M, 57 years

1st Line

Apr 2020 Aug 2020	**INDUCTION PHASE** Velcade-Thalidomide-Dexamethasone x 4 cycles
Nov 2020	**1° AUTOLOGOUS STEM CELLS TRANSPLANTATION**
Aug 2021	**2° AUTOLOGOUS STEM CELLS TRANSPLANTATION**
Nov 2021 Dec 2021	**CONSOLIDATION PHASE** Velcade-Thalidomide-Dexamethasone x 2 cycles
Jan 2022	**MAINTENANCE PHASE** Lenalidomide 10 mg (1-21 d/28 cycles)

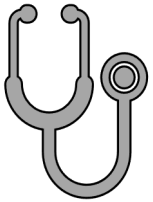
Best Response VGPR

CASE REPORT V.D.: M, 57 years

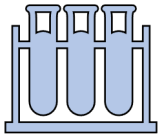
Dec 2022

MAINTENANCE PHASE
Lenalidomide 10 mg (1-21 d/28 cycles)

- **Shortness of breath and dyspnea**
- **Bone pain**



- ***Ntr***

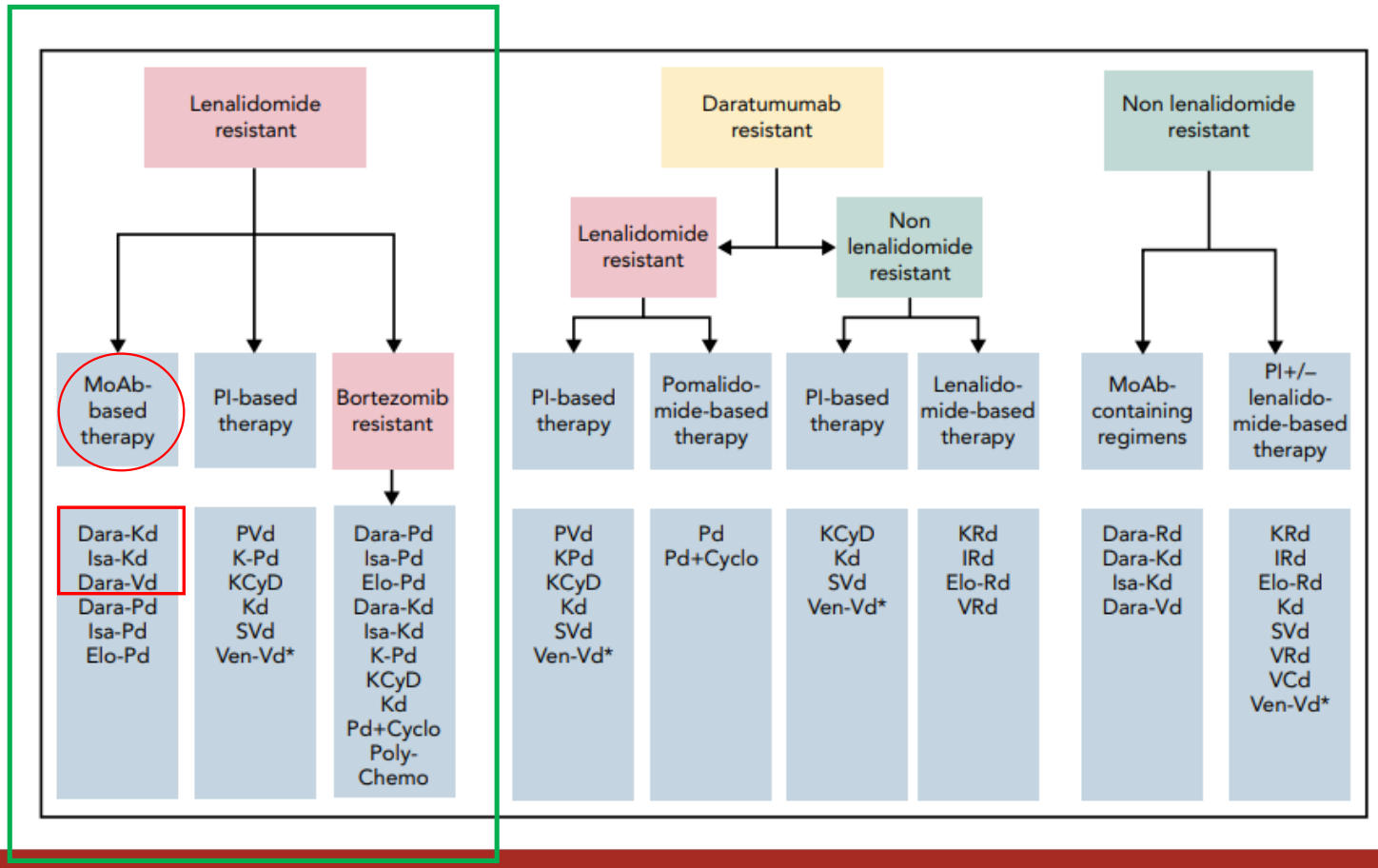


- **Paraprotein:** 2.9 g/dL
- **FLC kappa:** 1006 mg/L
- **K/L ratio:** 101
- **Bence Jones proteinuria**: 0.9 g/24h
- **Calcium and kidney function:** 13 mg/dl, 1.3 mg/dl
- **Blood count**: Hb 9.2 /dL; Platelets 162.000/µL

18F-FDG PET/TC increased uptake (pelvis, iliac wings, D11, **L3-L4**)

PROGRESSION DISEASE

APPROACH TO CHOICE OF REGIMENS AT FIRST RELAPSE ACCORDING TO RESISTANCE TO AGENTS USED AT FIRST LINE.



Kastritis, Blood 2022

APPROACH TO CHOICE OF REGIMENS AT FIRST RELAPSE ACCORDING TO RESISTANCE TO AGENTS USED AT FIRST LINE.

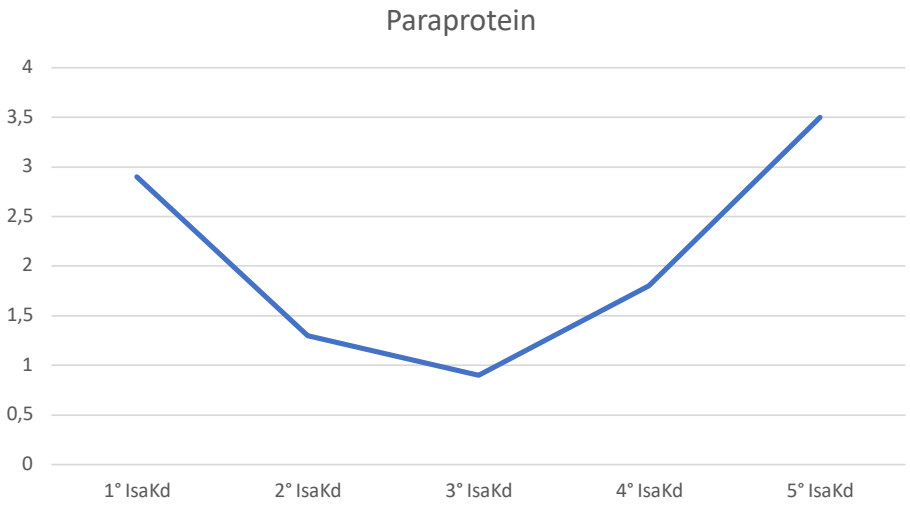
	R-free regimens						R-based regimens			
Efficacy data	**ENDEAVOR[1,2] Kd (464)**	**OPTIMISMM[3,4] PVd (281)**	**CASTOR[5,6] DaraVd (251)**	**APOLLO[7] DaraPd (151)**	**CANDOR[8-11] DaraKd (312)**	**IKEMA[12,13] IsaKd (179)**	**POLLUX[14-16] DaraRd (286)**	**ASPIRE[17,18] KRd (396)**	**TOURMALINE[19] IxaRd (360)**	**ELOQUENT-2[20-22] EloRd (319)**
No of median prior LOTs	2	2	2	2	2	2	1	2	-	2
Len-refractory, %	**24**	**71**	**24**	**79**	**32**	**32**	**0**	**7**	**0**	**NA**
≥ CR, %	**13**	**16**	**30**	**25**	**33**	**44**	**57**	**32**	**12**	**4**
MRD neg[10 -5] ITT, %	NA	NA	14	9	23	34	33	NA	NA	NA
mPFS ITT, months **(Δ mos) HR**	18.7 (Δ 9.3) 0.53	11.2 (Δ 4.1) 0.61	16.7 (Δ 9.6) 0.31	12.4 (Δ 5.5) 0.63	28.6 (Δ 13.4) 0.59	35.7 (Δ 16.5) 0.58	45.5 (Δ 27.0) 0.44	26.3 (Δ 8.7) 0.69	20.6 (Δ 5.9) 0.74	19.4 (Δ 4.5) 0.70
mPFS 1PLoT, months (Δ mos) HR	22.2 (Δ 12.1) 0.45	20.7 (Δ 9.1) 0.54	27.0 (Δ 19.1) 0.22	14.1 (Δ 1.5) 0.70	NR (Δ NR) 0.66	NR (Δ NR) 0.59	53.3 (Δ 33.7) 0.42	29.6 (Δ 12.0) 0.71	20.6 (Δ 4) 0.88	15.8 (Δ 3.7) 0.85
mPFS len-refr, months **(Δ mos) HR**	**8.6**	**9.5** (Δ 3.9) 0.65	**7.8** (Δ 2.9) 0.44	**9.9** (Δ 3.4) 0.66	**28.1** (Δ 17) 0.46	**NC** (Δ NC) 0.60	**NA**	**NA**	**NA**	**NA**

1. Dimopoulos MA, et al. *Lancet Oncol.* 2016;(1)17:27-38. 2. Moreau P, et al. *Leukemia.* 2017;31(1):115-122. 3. Richardson PG, et al. *Lancet Oncol.* 2019;20(6):781-794. 4. Dimopolous MA, et al. *Leukemia.* 2021; 35(6):1722–1731. 5. Mateos MV, et al. *Cl Lymph Myelom Leuk.* 2020;20(8):509-51. 6. Weisel KC, et al. ASH 2019. Abstract 3192. 7. Dimopoulos MA, et al. *Lancet Oncol.* 2021;22(6):801-12. 8. Dimopoulos MA, et al. *Lancet.* 2020;396(10245):186-197. 9. Dimopoulos MA, et al. ASH 2020. Abstract 2325. 10. Landgren O, et al. ASH 2020. Abstract 2282. 11. Usmani SZ, et al. Lancet Oncol. 2022;23(1):65-76. 12. Moreau P, et al. *Lancet.* 2021;397(10292):2361-2371. 13. Moreau P. ESMO 2022; Abstract VP5-2022. 14. Bahlis NJ, et al. *Leukemia.* 2020;34(7):1875-1884. 15. Kaufmann JL, et al. ASH 2019. Abstract 1866. 16. Loiseau HA, et al. *J Clin Oncol.* 2021;39(10):1139-1149. 17. Stewart AK, et al. *N Engl J Med.* 2015;372(2):142-152. 18. Dimopolous MA, et al. *Blood Cancer Journal.* 2017;7(4):E554. 19. Mateos MV, et al. *Haematologica* 2017 Volume 102(10):1767-1775. 20. Lonial S, et al. *N Engl J Med.* 2015;13;373(7):621-631. 21. Dimopoulos MA, et al. *Cancer.* 2018,124(20):4032-4043. 22. Lonial S, et al. *N Engl J Med.* 2015;13;373(7):621-631 (supplemental).

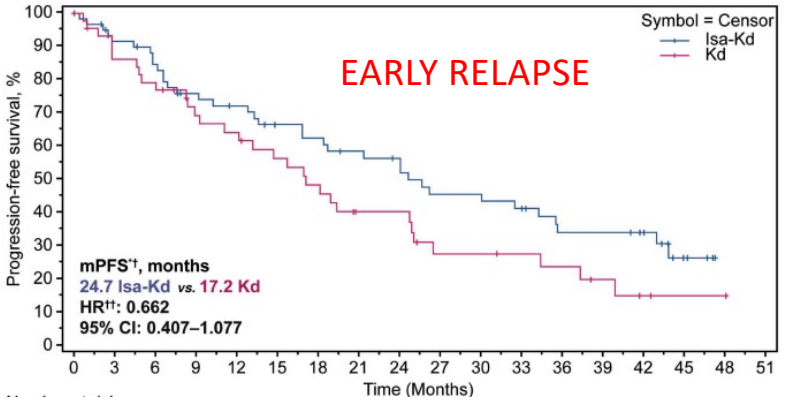
CASE REPORT V.D.: M, 57 years

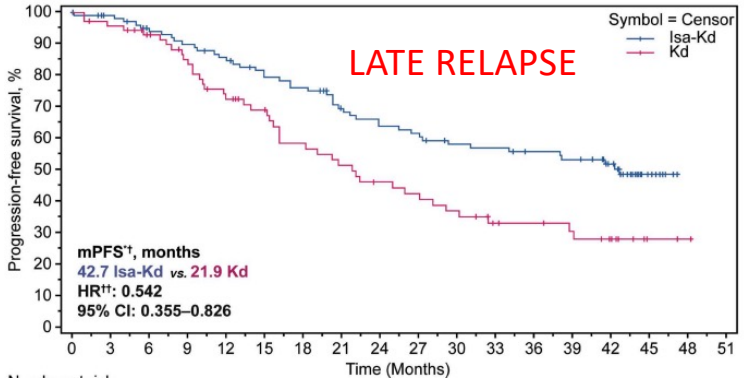
2° Line Jan 2023

ISATUXIMAB-CARFILZOMIB-DEXAMETHASONE (IsaKd)



PROGRESSION DISEASE





Facon et al Haematologica 2024

APPROACH TO CHOICE OF REGIMENS AT SECOND RELAPSE ACCORDING TO RESISTANCE TO AGENTS USED AT PREVIOUS LINES.

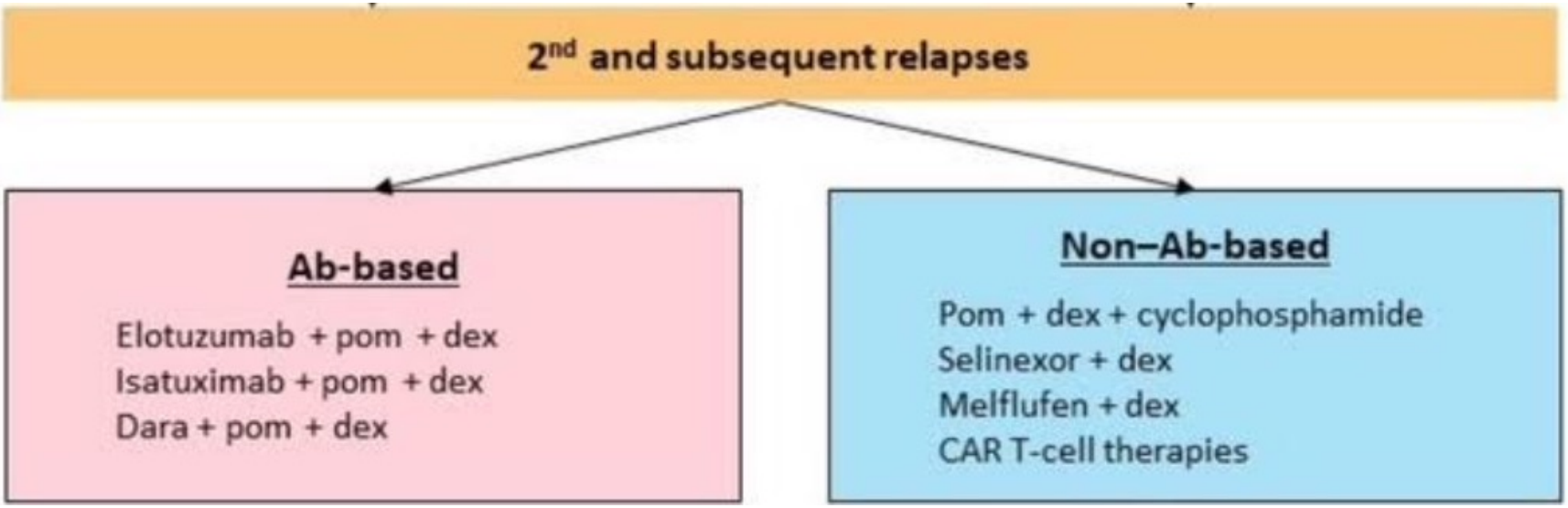


Figure adapted from: Dimopoulos MA, et al. *Ann Oncol*. 2021;32(3):309-322.

PHASE 2 AND 3 STUDIES OF POMALIDOMIDE-DEXAMETHASONE-BASED TRIPLETS

	Phase 3						Phase 2	
	PVd (OPTIMISMM)[1]		Isa-Pd (ICARIA)[2-4]		DaraPd (APOLLO)[5,6]		EloPd ELOQUENT-3[7]	
	PVd (N=281)	Vd (N=278)	Isa-Pd (N=154)	Pd (N=153)	DaraPd (N=151)	Pd (N=153)	EloPd (N=60)	Pd (N=57)
Median (range) prior lines, n	2 (IQR: 1-2)	2 (IQR: 1-2)	3 (2-11)	3 (2-10)	2 (1-5)	2 (1-5)	3 (2-8)	3 (2-8)
Median follow-up, months	15.9		11.6		30.7		9.1	
Len-refractory, %	71	69	94	92	79	80	90	84
Median PFS (len-ref), months	9.5	5.6	11.4	5.6	9.9	6.5	NA	NA
HR (95% CI)	0.65 (0.50-0.84)		0.59 (0.43-0.82)		0.64 (0.48-0.86)		NA	
Median PFS (len-ref at last line), months	NA	NA	11.6[b]	5.7[b]	NA	NA	NA	NA
HR (95% CI)	NA		0.50 (0.34-0.76)		NA		NA	
PI + len-ref, %	NA	NA	72	70	42	43	68	72
Median PFS (PI + len-ref), months	NA	NA	11.2	4.8	7.7[c]	6.1[c]	10.2	4.7
HR (95% CI)	NA		0.58 (0.40-0.84)		0.74 (0.49-1.12)[c]		0.56 (0.33-0.97)	
ORR, %	NA	NA	59.0	31.4	NA	NA	NA	NA
Safety								
Grade ≥3 AEs, %	NA	NA	87	71	89	82	57	60
Serious AEs, %	57	42	62	54	51	41	53	55

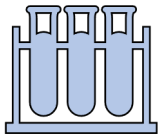
1. Richardson PG, et al. *Lancet Oncol* 2019;20(6):781-94. 2. Attal M, et al. *Lancet.* 2019;394(10214):2096-2107. 3. Bringhen S, et al. *Leuk Res.* 2021;104:106576. 4. Richardson PG, et al. *Lancet Oncol.* 2022;S1470-2045(22)00019-5. 5. Sonneveld P, et al. ASH 2021. Abstract 2747. 6. Dimopoulos MA, et al. *Lancet Oncol.* 2021;22(6):801-812. 7. Dimopoulos MA, et al. *N Engl J Med.* 2018;379(19):1811-1822. 8. Dimopoulos MA, et al. *N Engl J Med.* 2018;379(19):1811-1822(supplemental).

CASE REPORT V.D.: M, 57 years

3rd Line May 2023 — Elotuzumab-Pomalidomide-Dexamethasone (EloPd)

Oct 2023

18F-FDG PET/TC increased uptake (pelvis, iliac wings, D11, L3-L4, **D7-D8**)



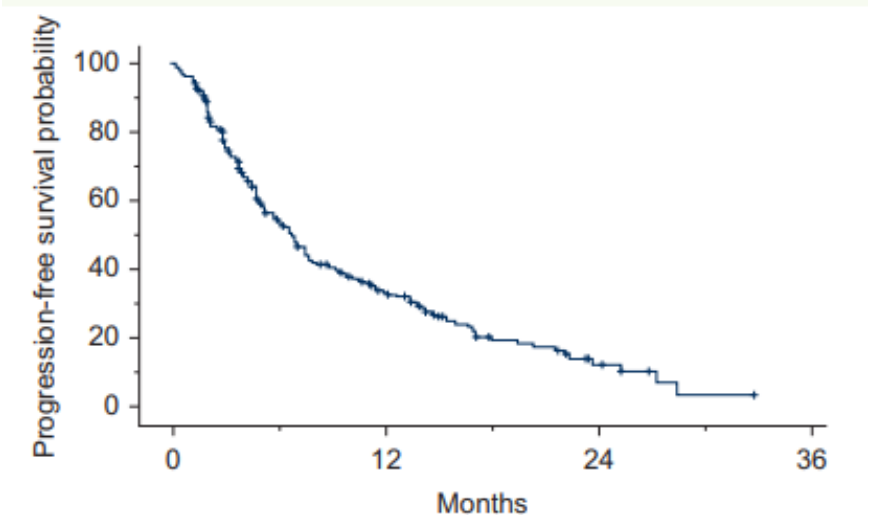
- **Calcium and kidney function:** 13 mg/dl, 1.2 mg/dl
- **Blood count**: Hb 8.5 /dL; Platelets 130.000/µL
- **Paraprotein:** 4.4 g/dL

PROGRESSION DISEASE

ORIGINAL ARTICLE

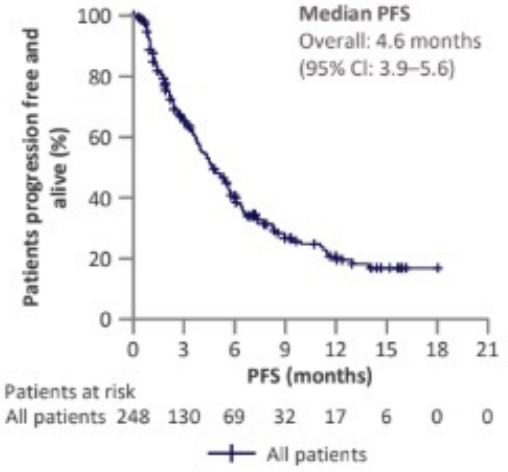
Outcomes and prognostic indicators in daratumumab-refractory multiple myeloma: a multicenter real-world study of elotuzumab, pomalidomide, and dexamethasone in 247 patients

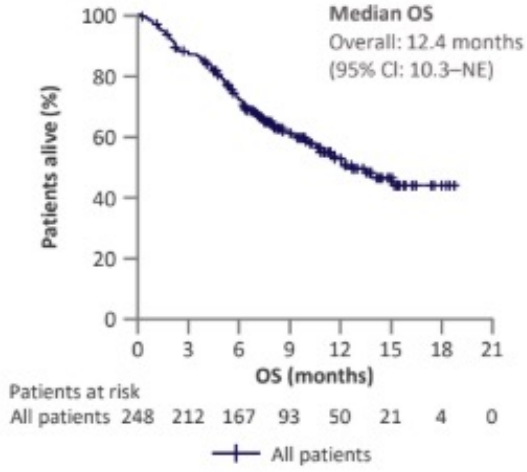
E. A. Martino[1], S. Palmieri[2], M. Galli[3], D. Derudas[4], R. Mina[5], R. Della Pepa[6], R. Zambello[7,8], E. Vigna[1], A. Bruzzese[1], S. Mangiacavalli[9], E. Zamagni[10,11], C. Califano[12], M. Musso[13], C. Conticello[14], C. Cerchione[15], G. Mele[16], N. Di Renzo[17], M. Offidani[18], G. Tarantini[19], G. M. Casaluci[20], A. Rago[21], R. Ria[22,23,24], G. Uccello[25], G. Barilà[26], G. Palumbo[27], L. Pettine[28], C. De Magistris[28], I. D. Vincelli[29], M. Brunori[30], F. Accardi[31], V. Amico[32], A. Amendola[33], R. Fontana[34], V. Bongarzoni[35], B. Rossini[36], E. Cotzia[37], A. Gozzetti[38], R. Rizzi[39,40], N. Sgherza[39], P. Curci[39], K. Mancuso[10,11], G. Reddiconto[17], A. Maroccia[41], L. Franceschini[42], G. Bertuglia[5], D. Nappi[15], E. Barbieri[43], M. Quaresima[43], M. T. Petrucci[44], F. Di Raimondo[14], A. Neri[45*], G. Tripepi[46], P. Musto[39,40], F. Morabito[47†] & M. Gentile[1,48*†]



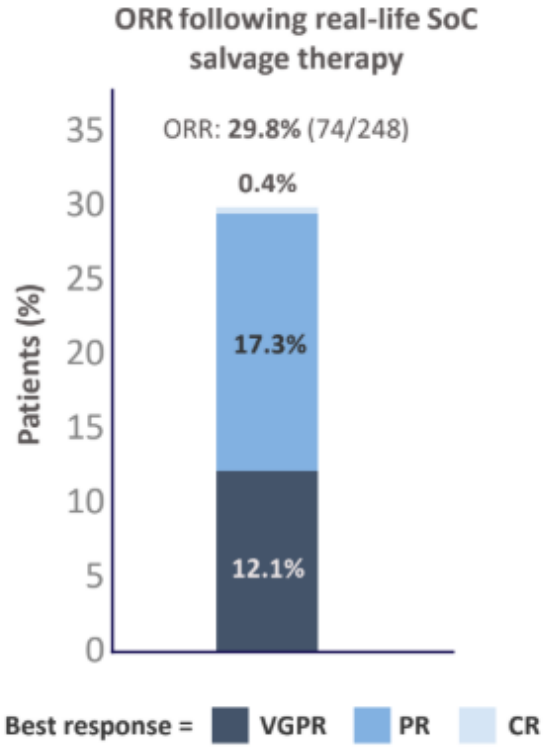
	Multivariable	
	HR (95% CI)	*P* value
Age (years)		
≤70		
>70		
Sex		
Female		
Male		
CrCl ml/min		
≥60		
<60		
LDH		
Normal		
Elevated		
Hb (g/l)		
≥9.5		
<9.5	1.43 (0.98-2.13)	0.075
International Staging System		
I		
II	1.66 (1.15-2.42)	**0.007**
III	1.82 (1.17-2.84)	**0.008**
Previous lines of therapy		
2		
>2		
Previous ASCT		
No		
Yes		
Daratumumab as last therapy		
Yes		
No	1.51 (1.06-2.17)	**0.023**
Proteasome inhibitor refractory		
No		
Yes		
Disease status		
Biochemical relapse		
Symptomatic relapse	1.63 (1.02-2.59)	**0.041**
Refractory to last treatment		
Cytogenetic analysis ($n = 99$)		
Standard risk		
High risk		

LocoMMotion: Poor outcomes of triple class exposed or refractory patients in the real world



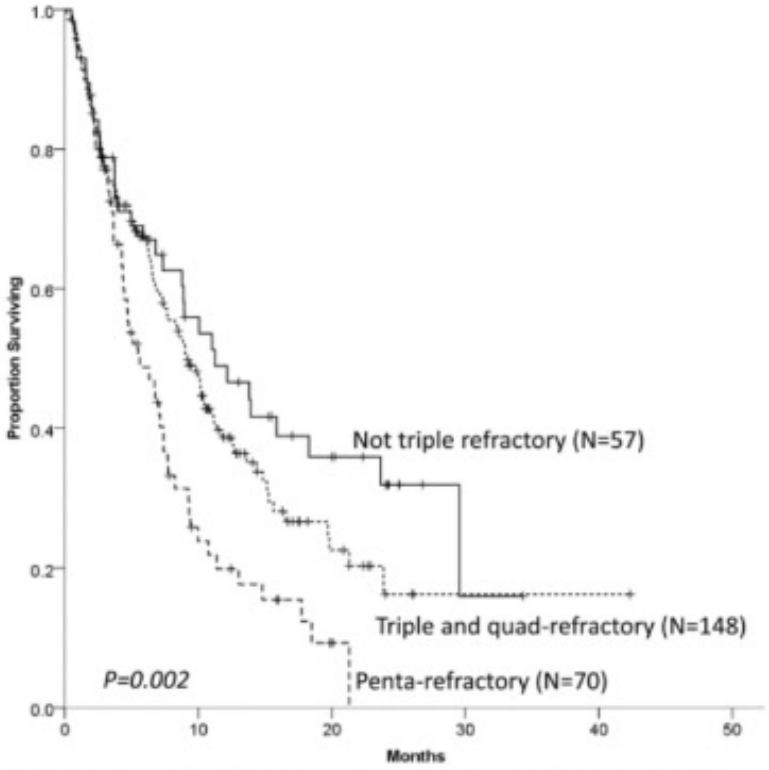


92 different treatment regimens were used;
160 patients (64.5%) had received ≥3 drugs,
demonstrating the lack of a defined SoC



Mateos MV, et al. Leukemia 2022;36:1371–1376.

MAMMOTH: Poor outcomes in patients refractory to CD38-targeted mAbs



mAb, monoclonal antibody; MAMMOTH, Monoclonal Antibodies in Multiple Myeloma: Outcomes after Therapy Failure; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.

- This multicentre, retrospective study investigated the natural history and outcomes of patients with MM **refractory to CD38-targeted mAbs**
- The poor outcomes observed in this study highlight the **unmet need for new strategies** to improve the survival of these patients

Response to first subsequent treatment regimen across all regimens (N=249)	
ORR, n (%)	78 (31.3)
Median PFS, months (95% CI)	3.4 (2.8–4.0)
Median OS, months (95% CI)	9.31 (8.1–10.6)

Median OS of 5.6 months for 'penta-refractory' patients

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

APPROACH TO CHOICE OF REGIMENS AT SUBSEQUENT RELAPSE ACCORDING TO RESISTANCE TO AGENTS USED AT PREVIOUS LINES.

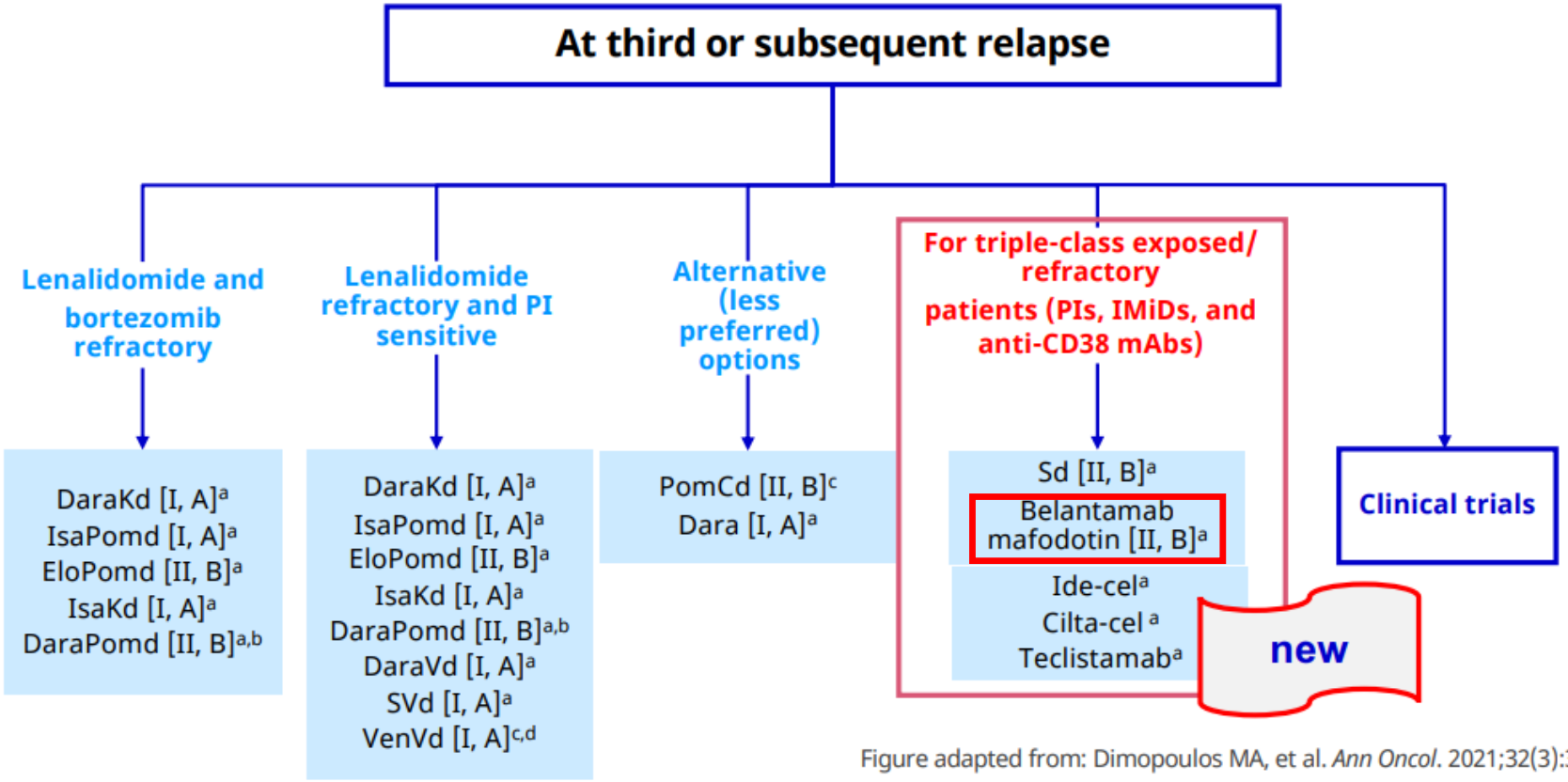
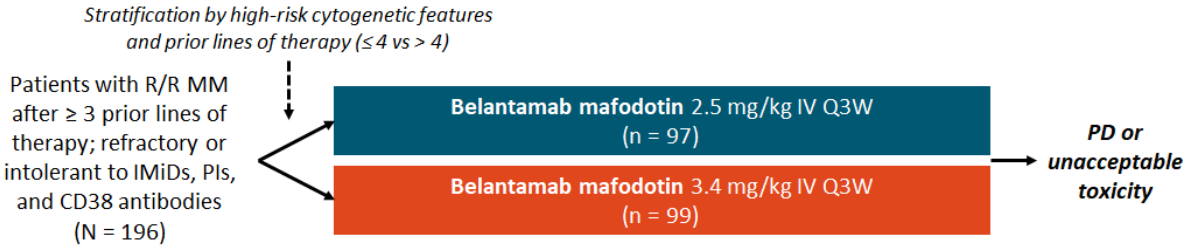


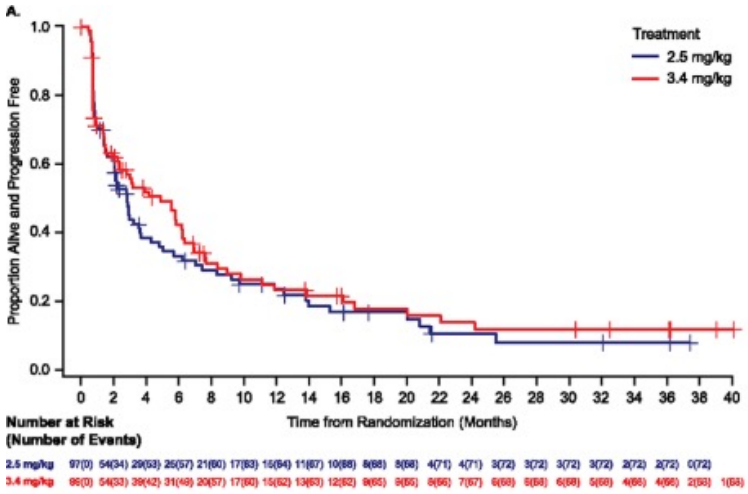
Figure adapted from: Dimopoulos MA, et al. *Ann Oncol*. 2021;32(3):309-322.[1]

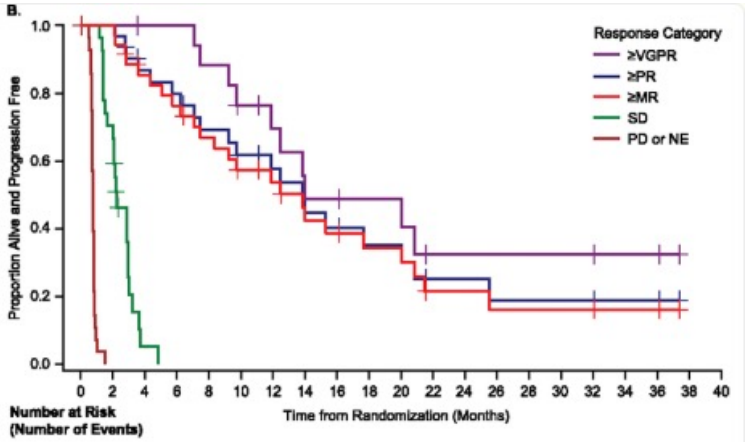
Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study

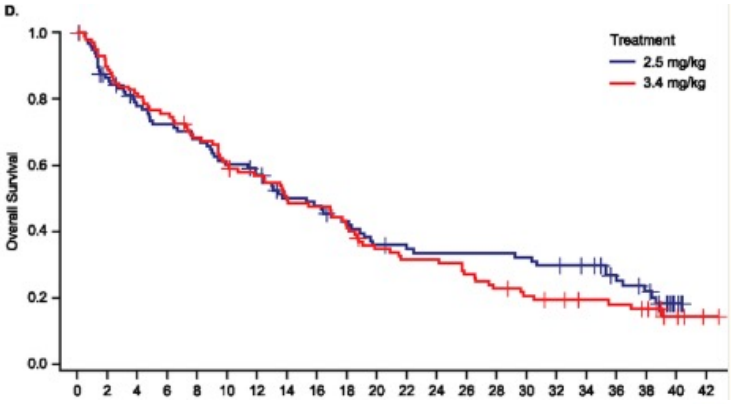
THE LANCET Oncology

Prof Sagar Lonial, MD [a] · Hans C Lee, MD [b] · Prof Ashraf Badros, MD [c] · Suzanne Trudel, MD [d] · Ajay K Nooka, MD [a] · Ajai Chari, MD [e] · et al. Show more







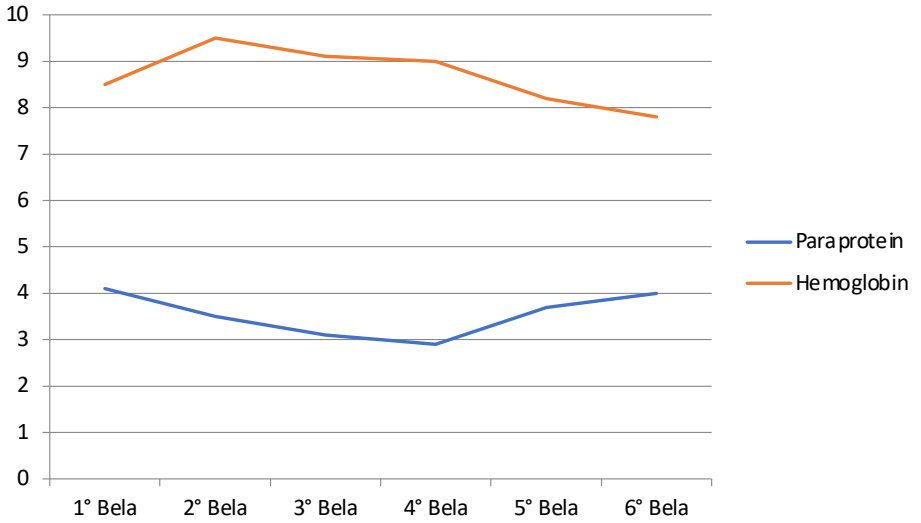


CASE REPORT V.D.: M, 57 years

4° Line Nov 2023

Belantamab single-agent

January 2024



- **Kidney function:** 2,4 mg/dl
- **Blood count**: Hb 7 /dL; Platelets 90.000/µL
- **Paraprotein:** 5,2 g/dL
- **Bence Jones proteinuria**: 2 g/24h

PROGRESSION DISEASE

APPROACH TO CHOICE OF REGIMENS AT SUBSEQUENT RELAPSE ACCORDING TO RESISTANCE TO AGENTS USED AT PREVIOUS LINES.

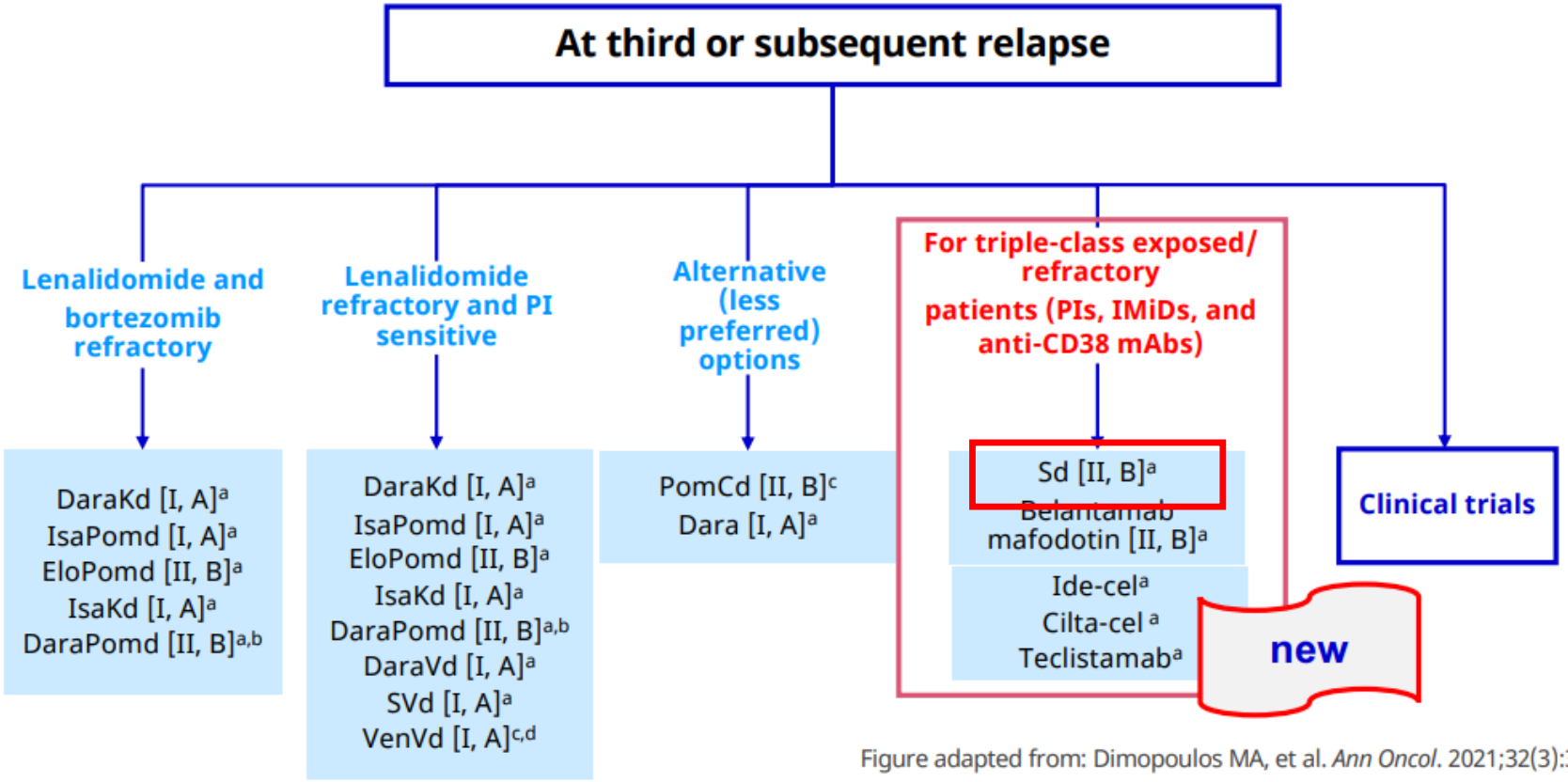


Figure adapted from: Dimopoulos MA, et al. *Ann Oncol*. 2021;32(3):309-322.[1]

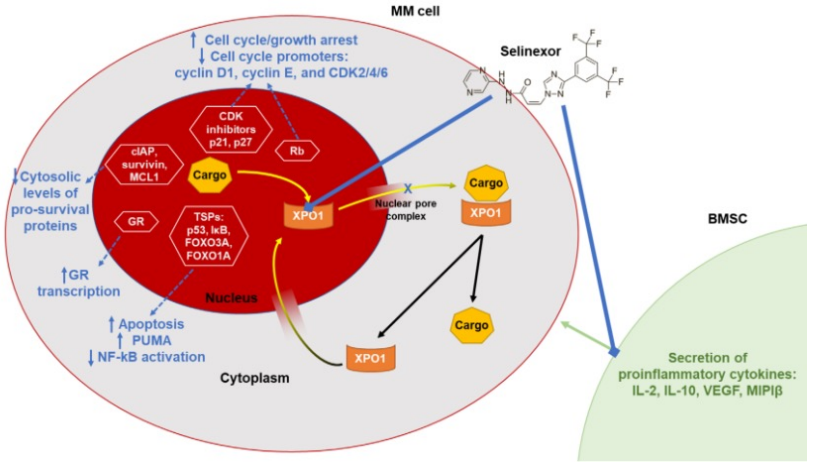
SELINEXOR selective inhibitor of nuclear export (SINE)

STORM TRIAL Chari. ASH 2018. Abstr 598

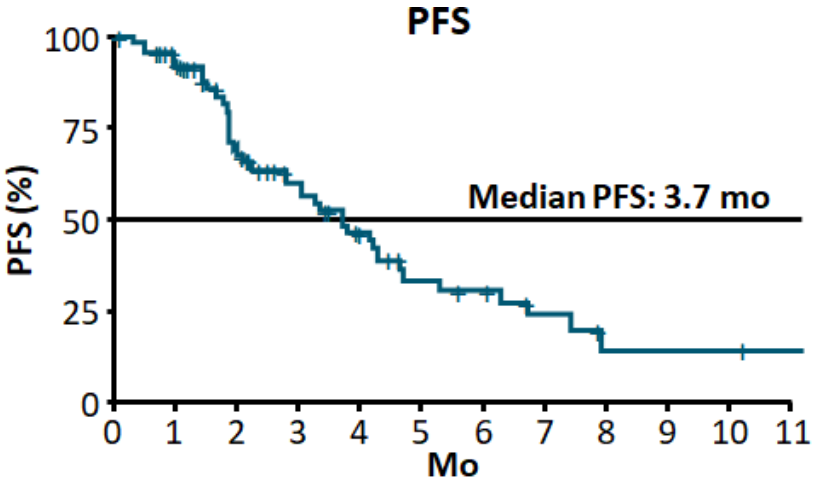
Treatment-experienced patients with penta-refractory MM* and adequate organ function† (N = 122)

→ **Selinexor** 80 mg PO + **Dexamethasone** 20 mg QW2 on Days 1, 3 of 28-day cycle

→ *Until PD*



- Median prior regimens: 7 (range: 3-18)
- Refractory
  - PI, IMiD, Dara: 100%
  - Car/Pom/Dara: 96%
  - Bort/Car/Len/Pom/Dara: 68%
- ORR: 26.2% (penta refractory: 25.3%)
- Median OS: 8.6 mo



CASE REPORT V.D.: M, 57 years

5° Line January 2024 — **SELINEXOR-DEXAMETHASONE (Sd) – CU**

	Hb (gr/dl)	Cr (mg/dl)	Par. (mg/dl)	P24 h
C1D1	7	2.4	5.2	2.1

SIDE EFFECTS
Nausea G1

→
- Continued Selinexor
- Supportive care

C2D1	7.8	2	4.9	1.9

SIDE EFFECTS
Nausea G3
Hyponatremia G3 (128 mmol/L)

→
- Interrupt Selinexor
- Supportive care

→ **Restart Selinexor (at 1 dose level lower)**
REDUCTION OF DOSAGE:
100 mg/w → 80 mg/w

C3D1	8.5	1.6	3	1.3
C4D1	7	1.5	4.2	1.2

DEATH

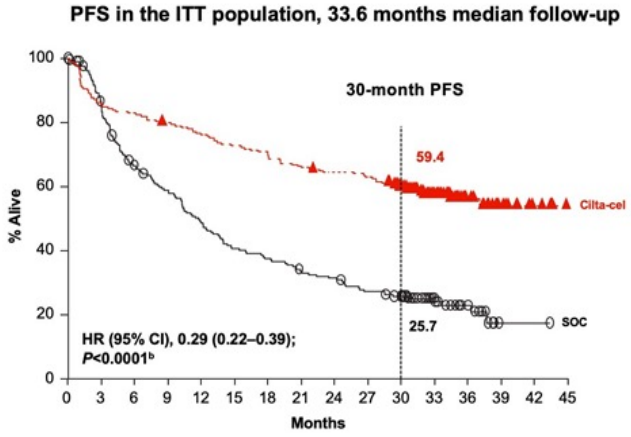
CONCLUSIONS

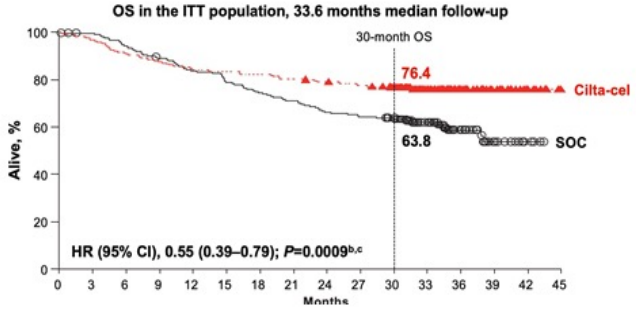
- Highly effective therapies for RRMM are helping to control the disease for our patients providing the benefits of improved survival and maintained the quality of life. Relapses continue to occur which is a humbling reminder that the disease remains much smarter than we are as clinicians and researchers.

- It is well established that next-generation IMIDs such as POM, next-generation PIs such as CAR and IXA, and monoclonals such as DARA, ISA, and ELO will continue to have substantial roles long term in the relapse/refractory setting.

- There is promise on the horizon as we race toward a functional cure for myeloma patients, with novel agents such as CAR-T and BITEs showing impressive activity in the most heavy of pre-treated patients.

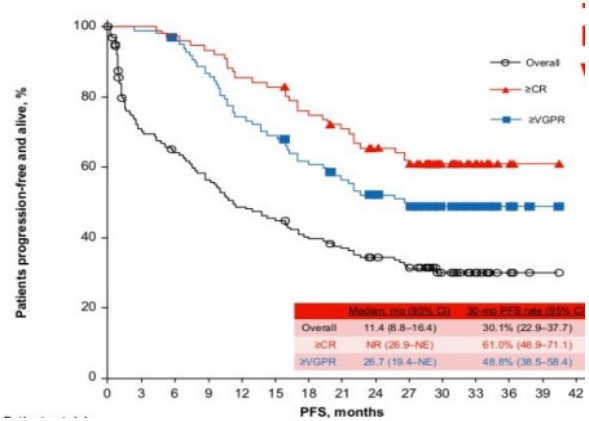
CILTA-CEL
CAR-T

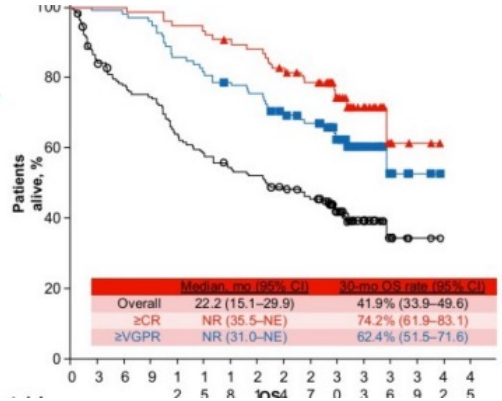




Mateos MV et al, IMS 2024 San Miguel J et al, NEJM 2023

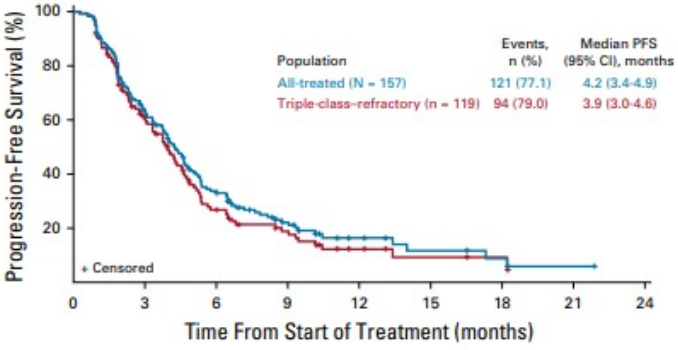
TECLISTAMAB
BISPECIFIC MoAb

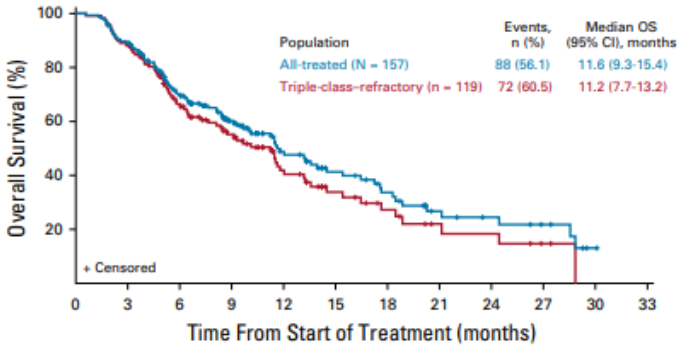




Garfall AL et al, ASCO 2024. P7540

MELFUFLEN
Peptide Drug Conj





Richardson, JCO 2021

Thank you!