ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Mieloma Multiplo: Stato dell'Arte

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Disclosures - M Cavo

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Employee	No relevant conflicts of interest to declare
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Speakers Bureau	Janssen, Celgene, Amgen, Sanofi
Honoraria	Janssen, Bristol-Myers Squibb, Amgen, Sanofi, GSK, Novartis, Pfizer, Takeda
Scientific Advisory Board	Janssen, Bristol-Myers Squibb, GSK, Amgen, Sanofi, Pfizer

Presentation includes discussion of the off-label use of a drug or drugs

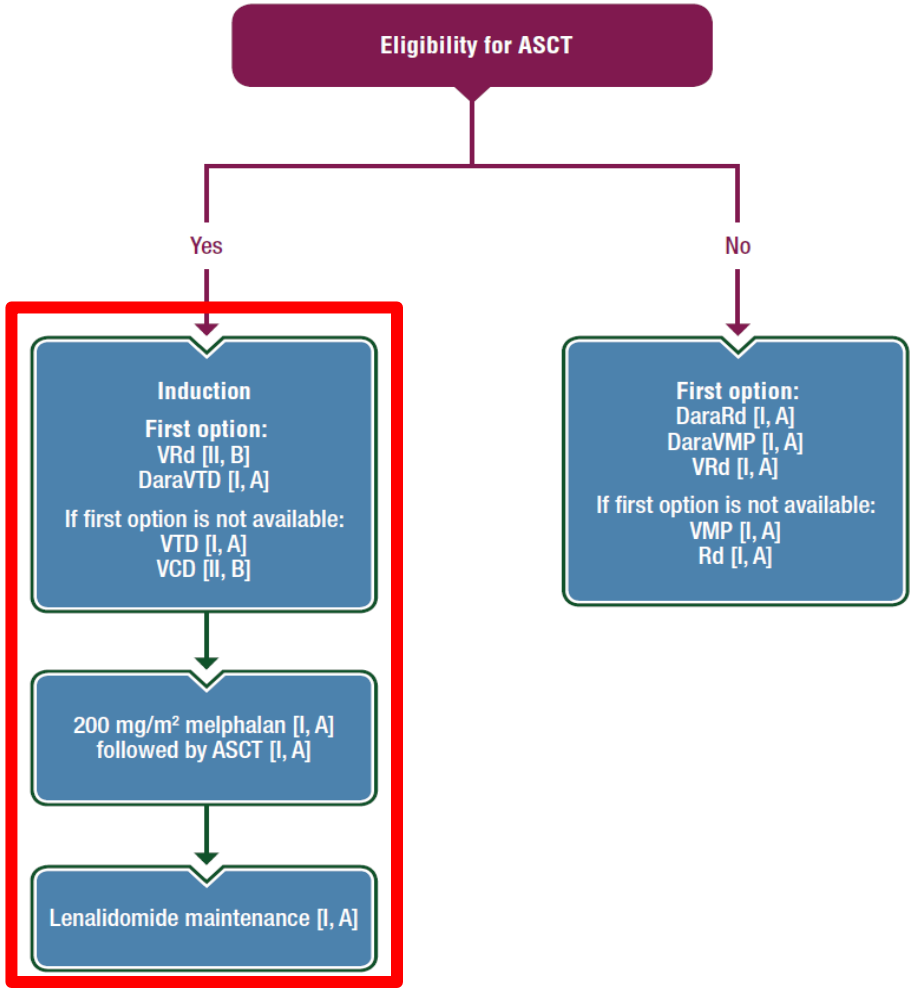
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

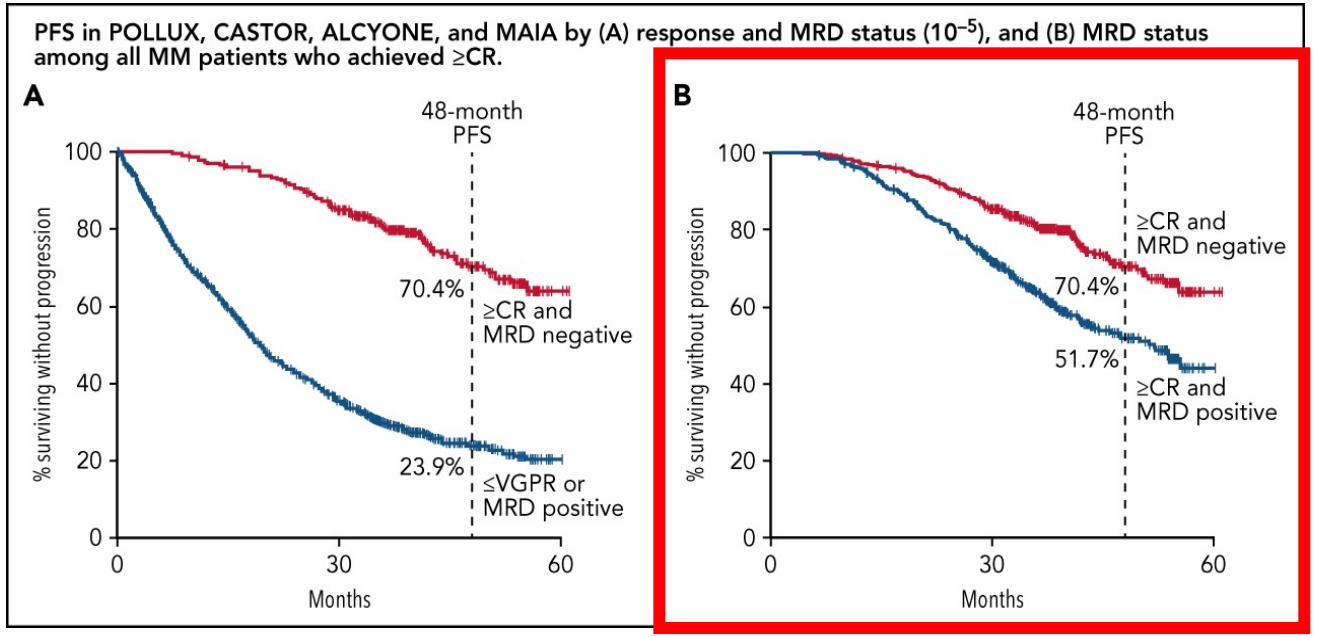
M. A. Dimopoulos[1], P. Moreau[2], E. Terpos[1], M. V. Mateos[3], S. Zweegman[4], G. Cook[5], M. Delforge[6], R. Hájek[7], F. Schjesvold[8,9], M. Cavo[10], H. Goldschmidt[11], T. Facon[12], H. Einsele[13], M. Boccadoro[14], J. San-Miguel[15], P. Sonneveld[16] & U. Mey[17], on behalf of the EHA Guidelines Committee* and ESMO Guidelines Committee*



Treatment endpoints

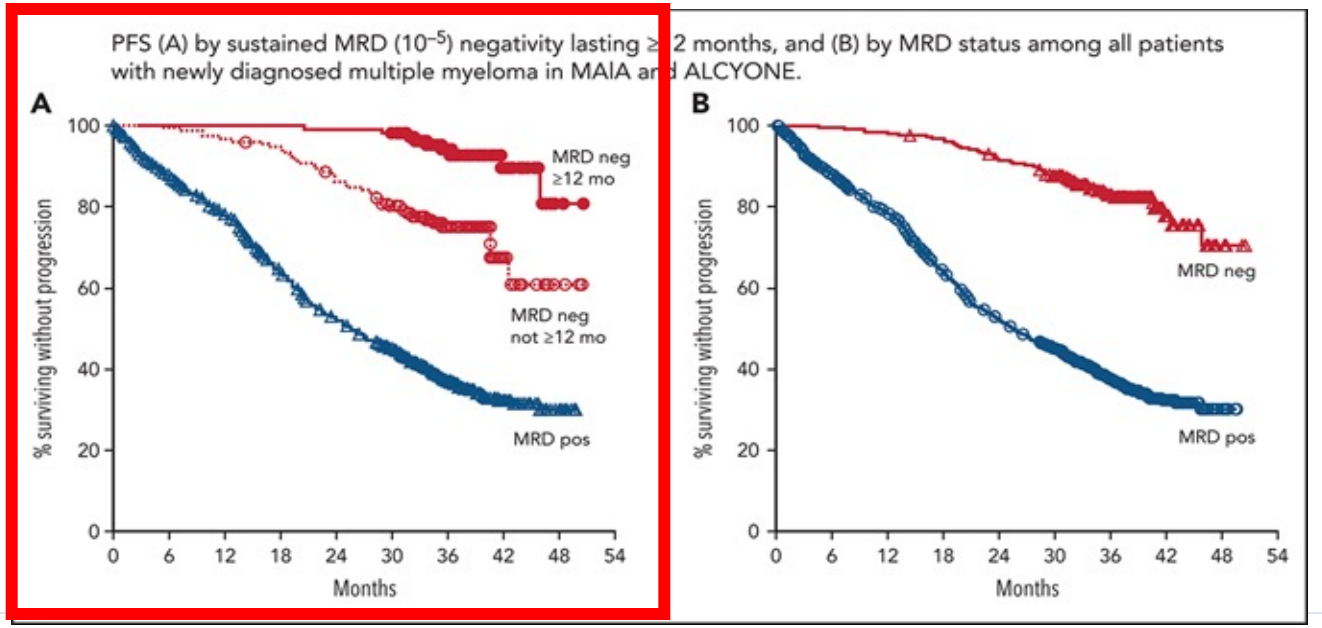
- **To maximize the rate of undetectable MRD**
- **To sustain MRD negativity**
- To prolong PFS/OS, offering a chance of cure (to a fraction of patients)
- To inform clinical decisions and tailor treatment

Undetectable MRD and sustained MRD negativity



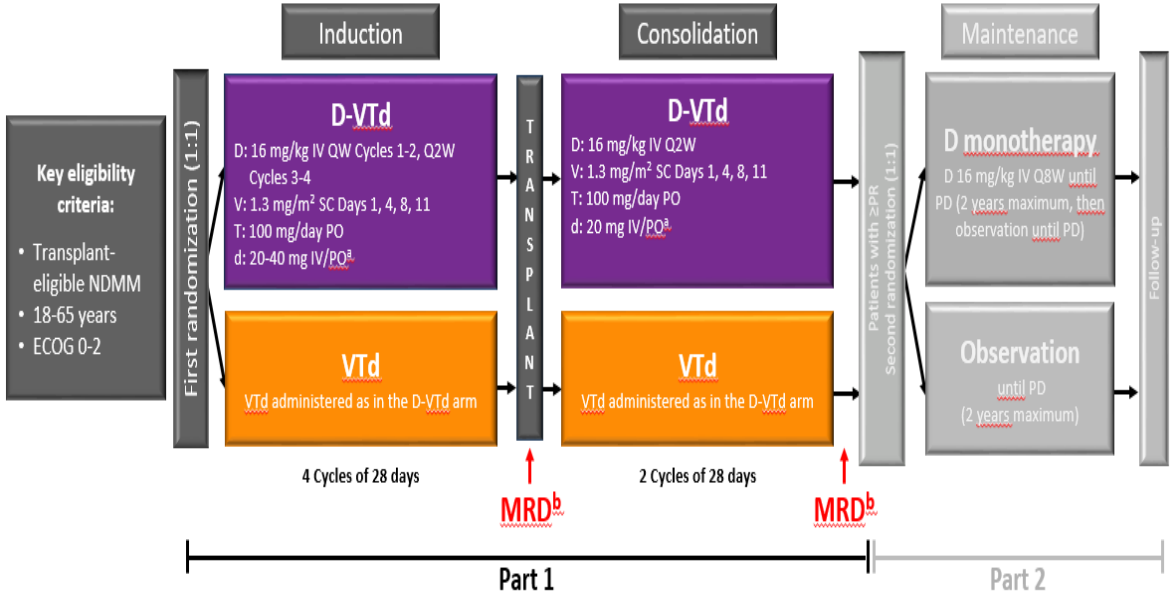
POLLUX+CASTOR + MAIA+ALCYONE

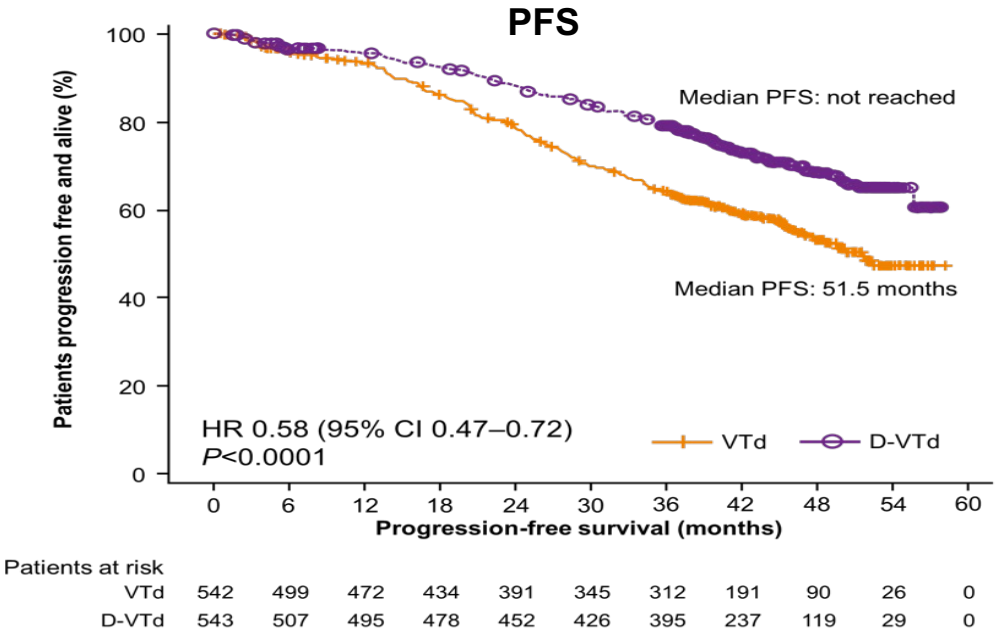
MAIA+ALCYONE

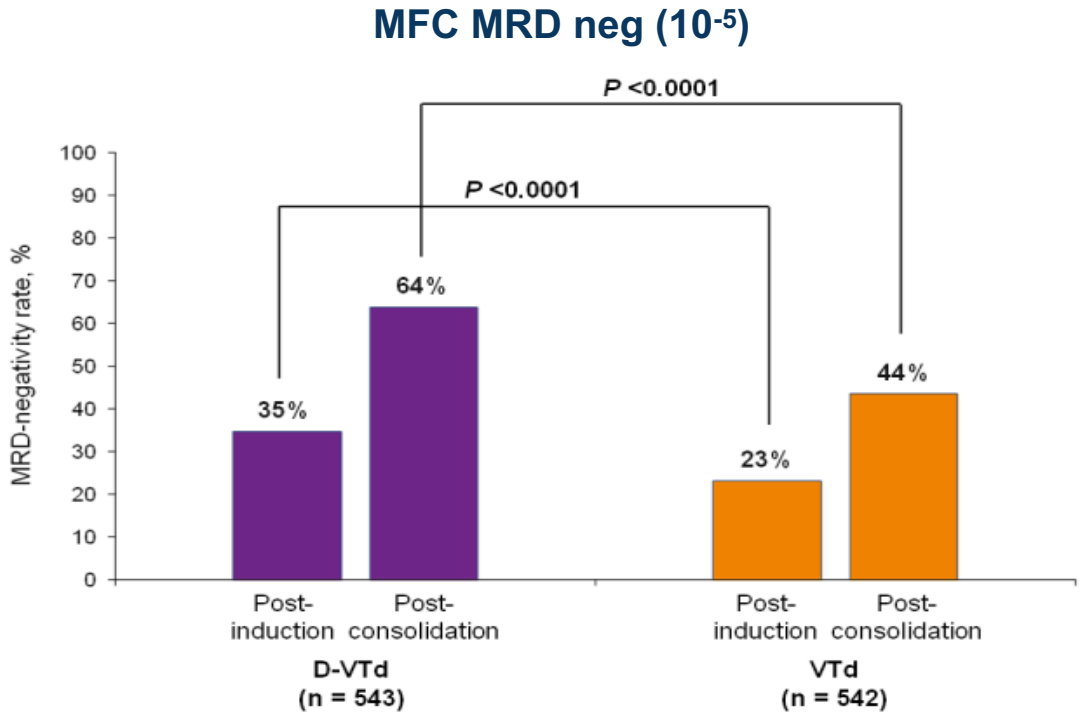


Cavo M et al, Blood 2022;139:835-44; San Miguel J et al, Blood 2022;139:492-501

Cassiopeia Study: Dara-VTD





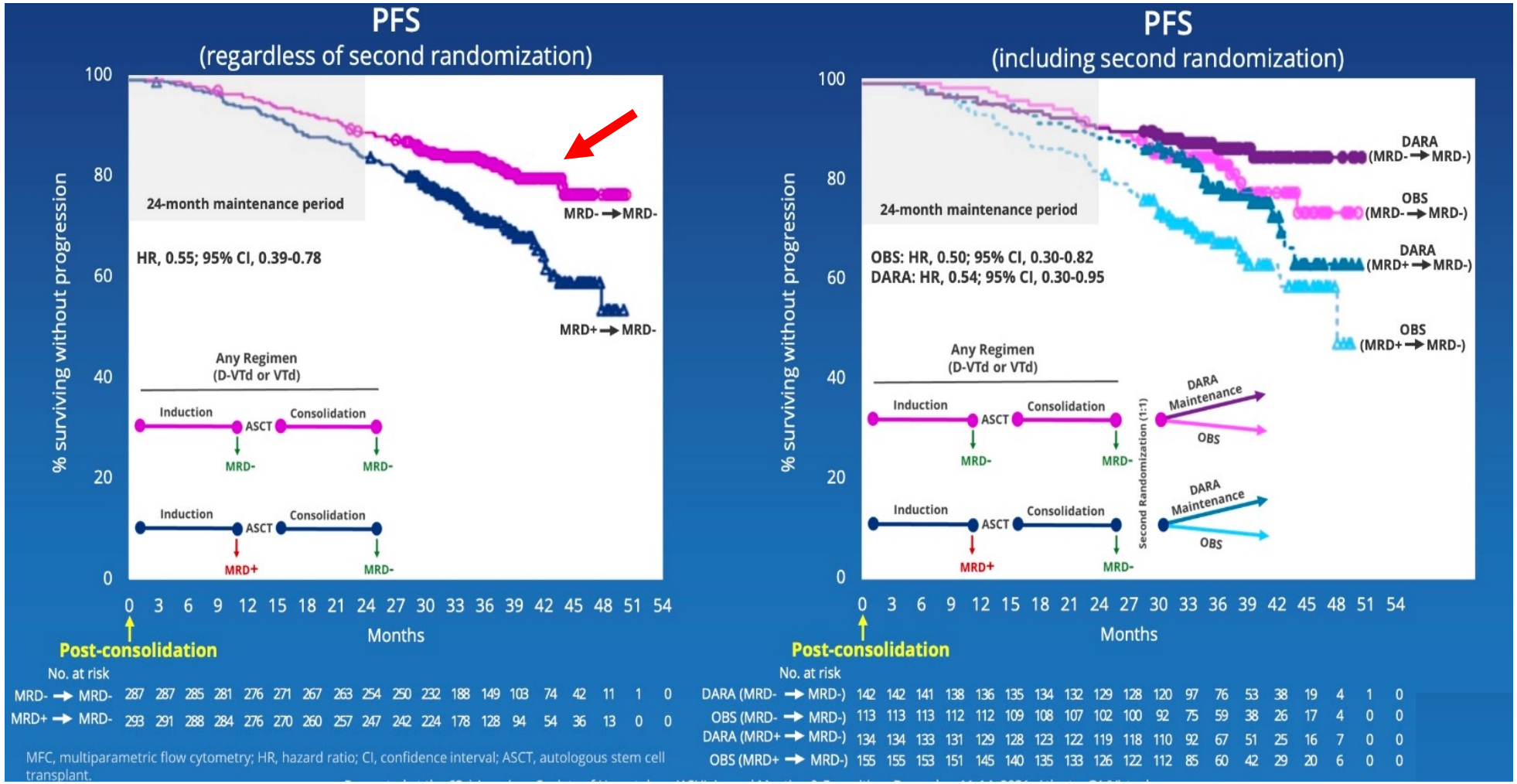


PBSC Collection and ASCT

	D-VTd	VTd
Pts receiving plerixafor, n (%)	110 (22)	39 (8)
CD34⁺ cells collected, mean (10^6/kg)	6.7	10.0
Pts with 1 day of apheresis, n (%)	184 (36.5)	327 (67)
Pts receiving transplant, n (%)	489 (97)	484 (99)
Pts achieving hematopoietic reconstitution, n (%)	488 (100)	482 (100)

1.Moreau P et al, Lancet 2019; 394: 29-38; Lancet Oncol 2021; 22:1378-90 2.Hulin C et al, Haematologica 2021; 106: -2260

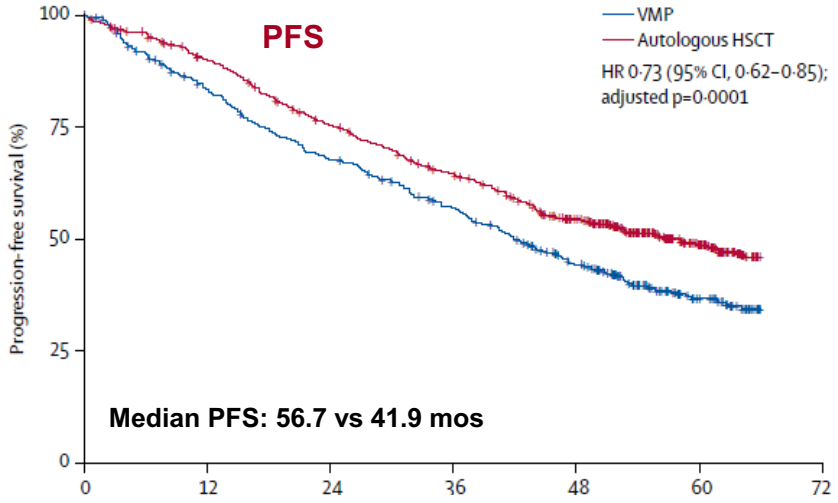
MRD dynamics after induction and consolidation

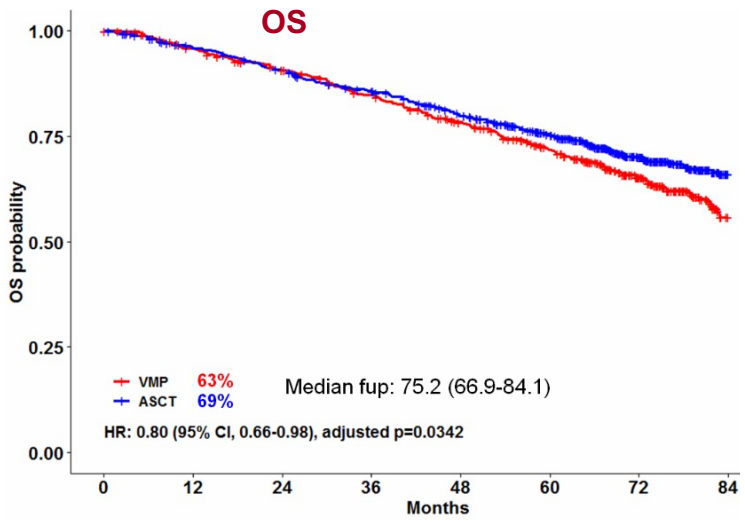


Patients who achieved MRD-negativity post-induction and maintained MRD negativity post-consolidation had improved PFS

Avet Loiseau H, et al. Blood 2021;138 (Suppl 1):82 (oral presentation).

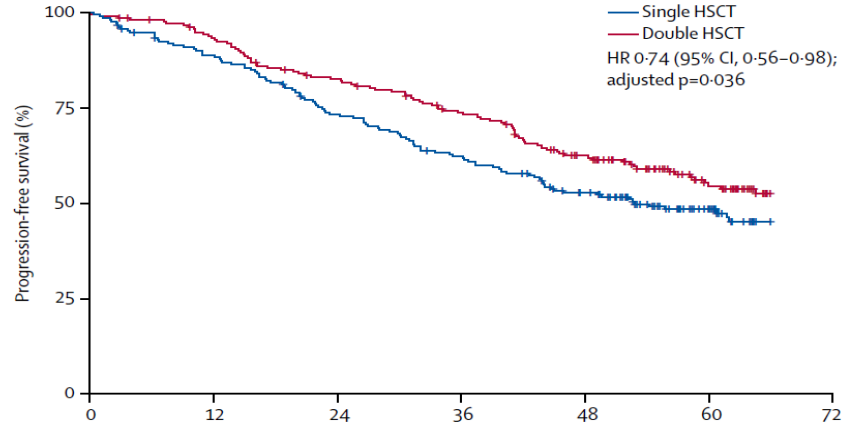
ASCT vs VMP upfront: clinical outcomes





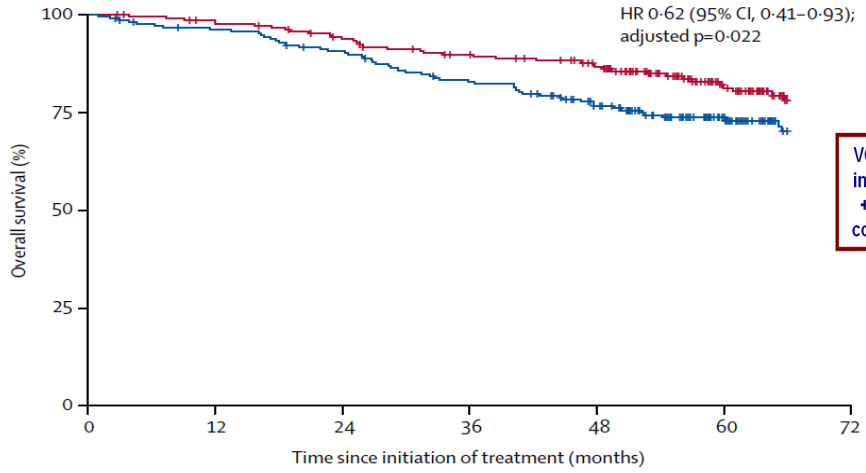
EMN02/HO95 phase 3 study

VCD (x 4) induction + PBSC collection → R1 → VMP x 4 cycles / HDM + ASCT (single/double) → R2 → VRD consolidation x 2 cycles / No consolidation → Maintenance lenalidomide



Number at risk (number censored)

Double HSCT	210 (0)	192 (4)	167 (7)	145 (11)	115 (19)	68 (54)	..
Single HSCT	209 (0)	181 (5)	147 (7)	124 (8)	97 (16)	53 (54)	..



Number at risk (number censored)

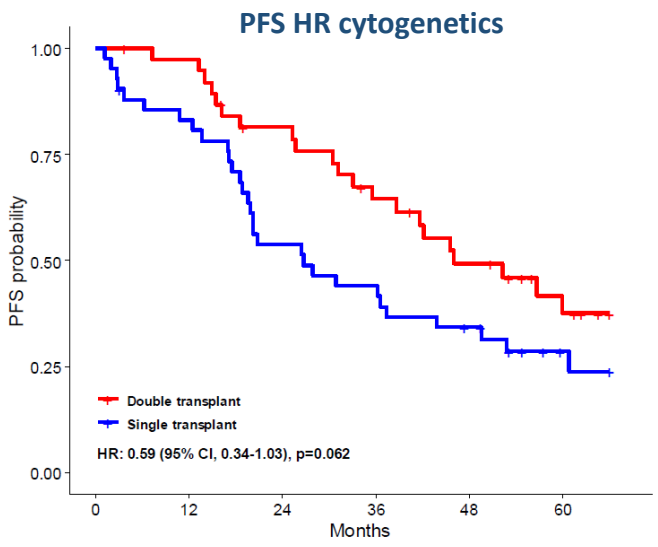
Double HSCT	210 (0)	201 (4)	189 (8)	175 (15)	159 (24)	100 (75)	..
Single HSCT	209 (0)	195 (6)	182 (8)	164 (10)	141 (21)	85 (72)	..

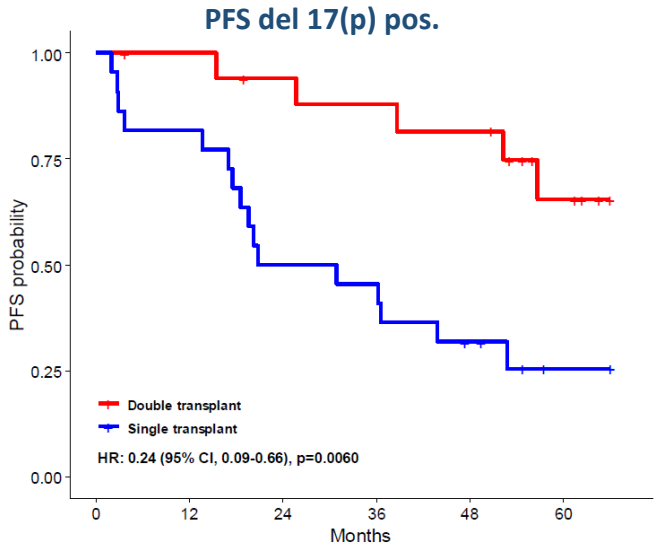
EMN02/HO95 phase 3 study

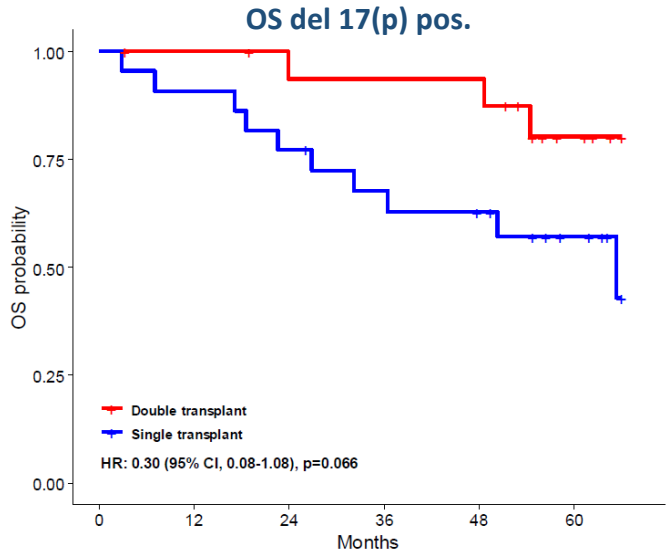
VCD (x 4) induction + PBSC collection → R1 → VMP x 4 cycles / HDM + ASCT (single/double) → R2 → VRD consolidation x 2 cycles / No consolidation → Maintenance lenalidomide

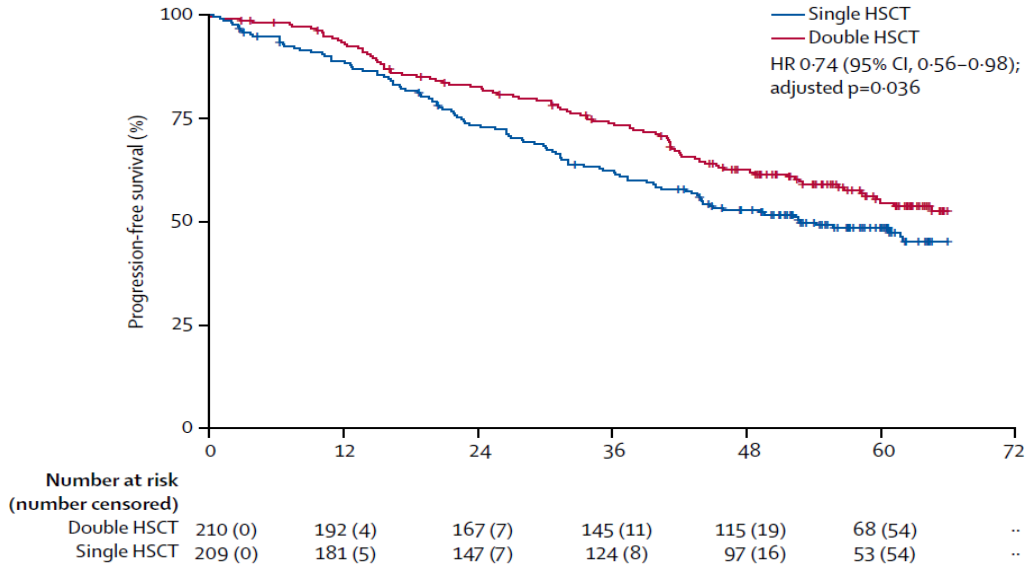
1.Cavo M et al. Lancet Haematol 2020;7: e456-68; 2. Cavo M et al, Blood 2020; 136 (Suppl.1): Abstract 142

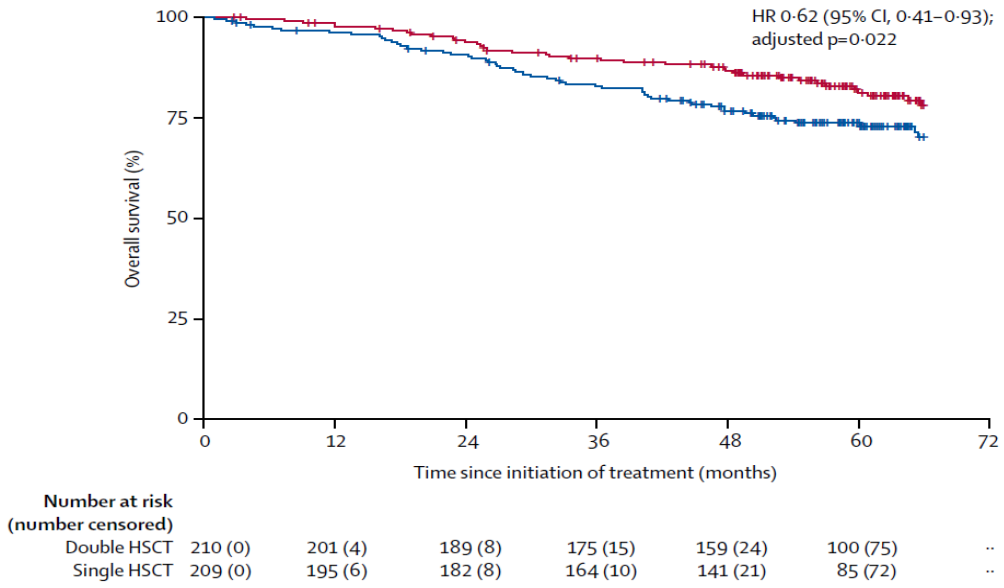
Single vs Double ASCT upfront: clinical outcomes











1.Cavo M et al. Lancet Haematol 2020;7: e456-68

Defining the optimal duration of len maintenance

EMA approval: lenalidomide at 10-15 mg daily until PD

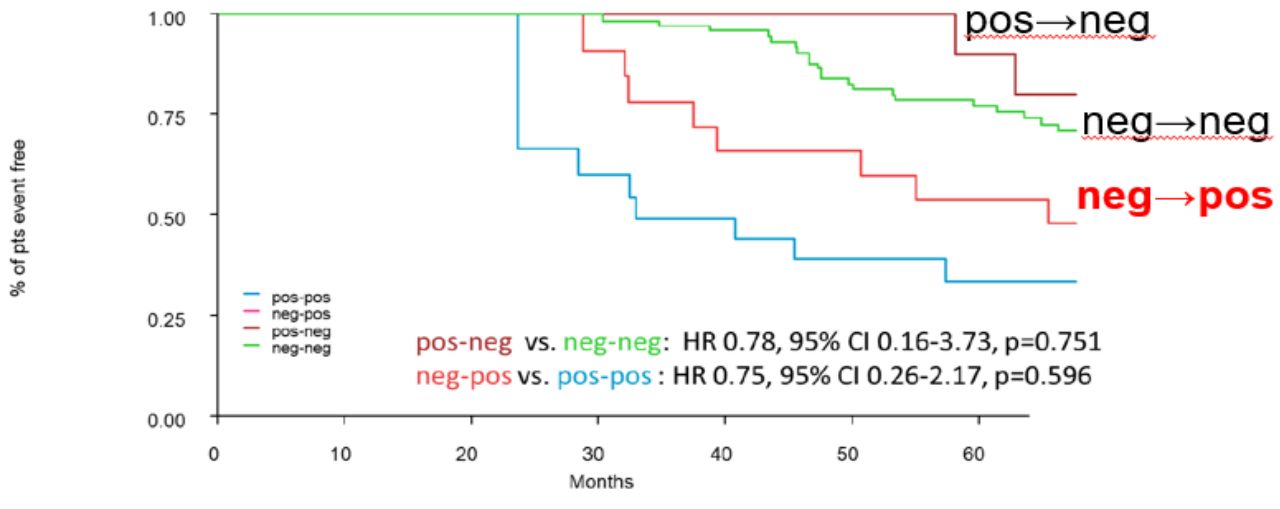
Table 2. Duration of Maintenance Therapy (safety population)

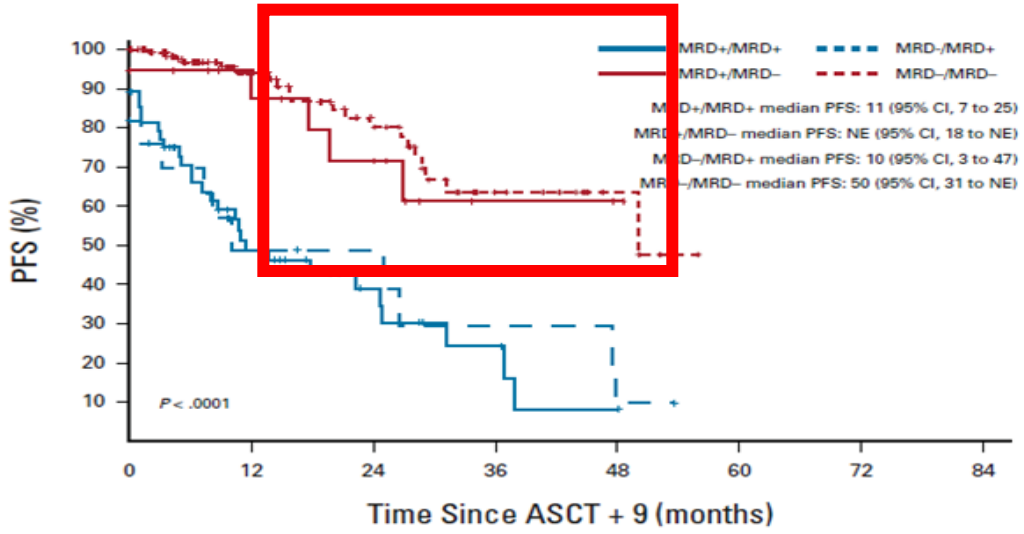
	CALGB			IFM*			GIMEMA		Pooled	
		Placebo (n = 221)		Len Maintenance (n = 306)						
Treatment Duration	Len Maintenance (n = 224)	Placebo Up to Crossover (n = 221)	Len After Crossover (n = 76)†	All Patients (n = 306)	Cohort Treatment Stopped Jan 2011 (n = 119)‡	Placebo (n = 302)	Len Maintenance (n = 56)	Observation (n = 67)	Len Maintenance (n = 586)	Placebo or Observation (n = 590)
Mean, months (range)§	30 (0-108)	13 (0-51)	25 (0-61)	25 (0-55)	39 (27-55)	20 (0-49)	35 (2-71)	29 (0-75)	28 (0-108)	22 (0-86)
Duration category, No. (%)										
≥ 1 year	150 (67.0)	95 (43.0)	46 (60.5)	217 (70.9)	119 (100)	211 (69.9)	44 (78.6)	51 (76.1)	411 (70.1)	391 (66.3)
≥ 2 years	116 (51.8)	32 (14.5)	33 (43.4)	170 (55.6)	119 (100)	121 (40.1)	33 (58.9)	36 (53.7)	319 (54.4)	230 (39.0)
≥ 3 years	82 (36.6)	6 (2.7)	24 (31.6)	88 (28.8)	74 (62.2)	32 (10.6)	29 (51.8)	23 (34.3)	199 (34.0)	95 (16.1)
≥ 4 years	54 (24.1)	1 (0.5)	18 (23.7)	11 (3.6)	11 (9.2)	2 (0.7)	24 (42.9)	17 (25.4)	89 (15.2)	44 (7.5)

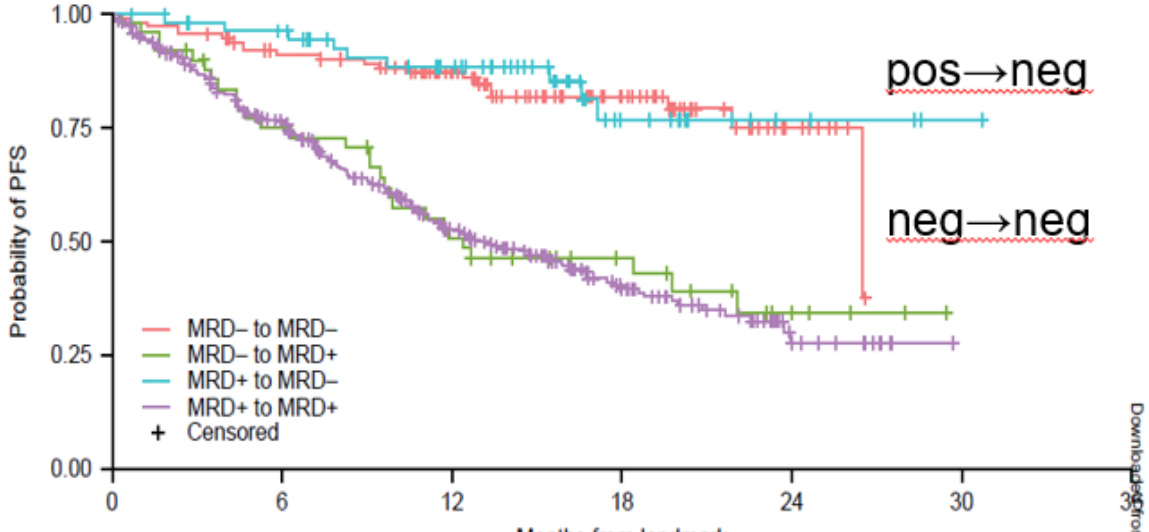
Is fixed treatment duration as effective as continuous treatment?
Which patients are more likely to benefit from one treatment vs another?

McCarthy PL, et al. J Clin Oncol. 2017 July 25; Cavo M. Personal Communication

Outcomes by MRD dynamics







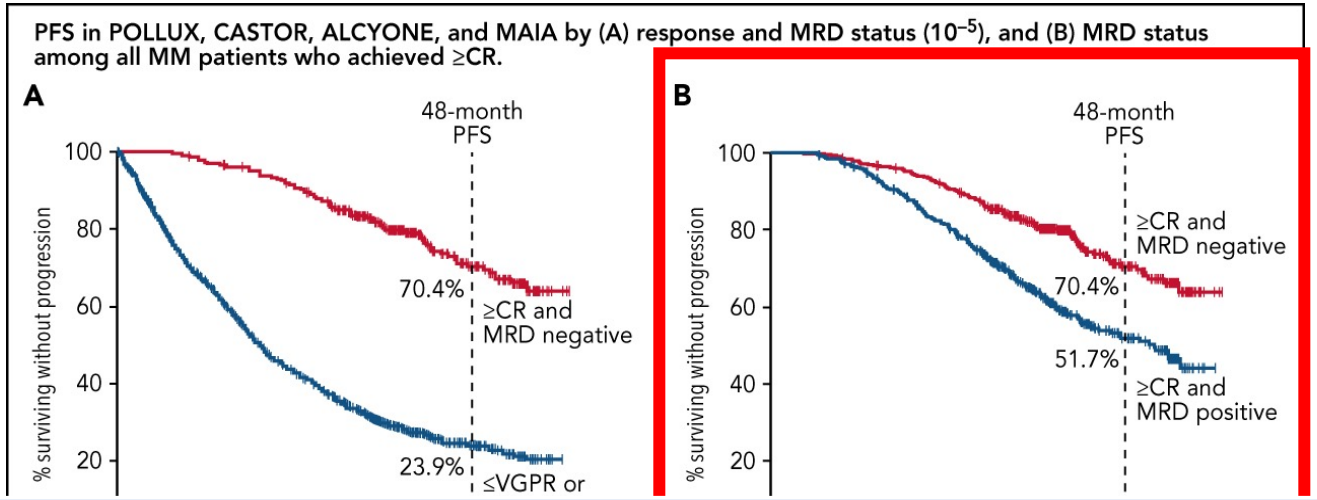
Patients at risk, n

MRD– to MRD–	114	97	70	40	9	0
MRD– to MRD+	50	35	23	14	4	0
MRD+ to MRD–	58	52	40	14	4	1
MRD+ to MRD+	365	241	129	50	10	0

Patients	n	Events	Median follow up, months (95% CI)	Median PFS, months (95% CI)	2-year PFS rate, % (95% CI)	HR (95% CI)	P value
MRD– to MRD–	114	21	16.8 (14.6-18.4)	26.5 (26.5-NR)	75.0 (64.1-87.8)	3.31 (1.77-6.20)	< .001
MRD– to MRD+	50	28	20.4 16.2-23.3)	12.4 (9.6-NR)	34.2 (21.4-54.8)		
MRD+ to MRD–	58	9	16.1 (14.1-17.4)	NR (NR-NR)	76.8 (63.5-92.8)	3.72 (1.85-7.46)	< .001
MRD+ to MRD+	365	182	15.2 (13.9-16.3)	12.9 (11.2-16.7)	27.6 (20.1-37.8)		

1. Oliva S et al. Blood Canc. J 2021 Jun 3;11(6):106; 2. de Tute RM et al, J Clin Oncol 2022; April 4, Online ahead of print ; 3. Paiva B. et al, Blood 2022 Sep 21;blood.2022016782

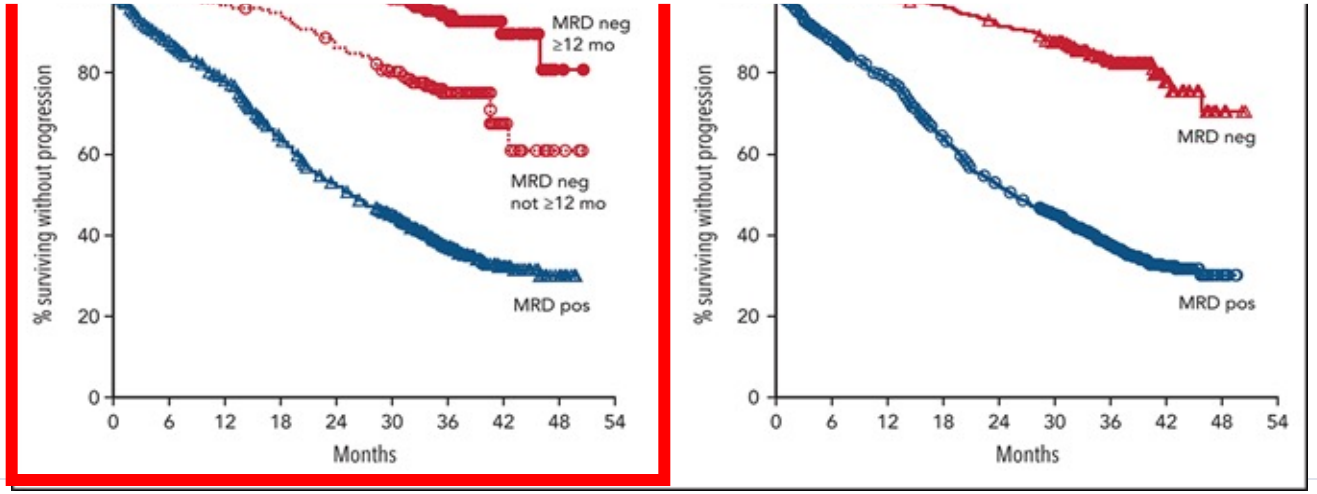
Undetectable MRD and sustained MRD negativity



POLLUX+CASTOR + MAIA+ALCYONE

MRD status changes during treatment. Monitoring MRD dynamics is likely to provide a more detailed risk prediction

MAIA+ALCYONE



Cavo M et al, Blood 2022;139:835-44; San Miguel J et al, Blood 2022;139:492-501

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Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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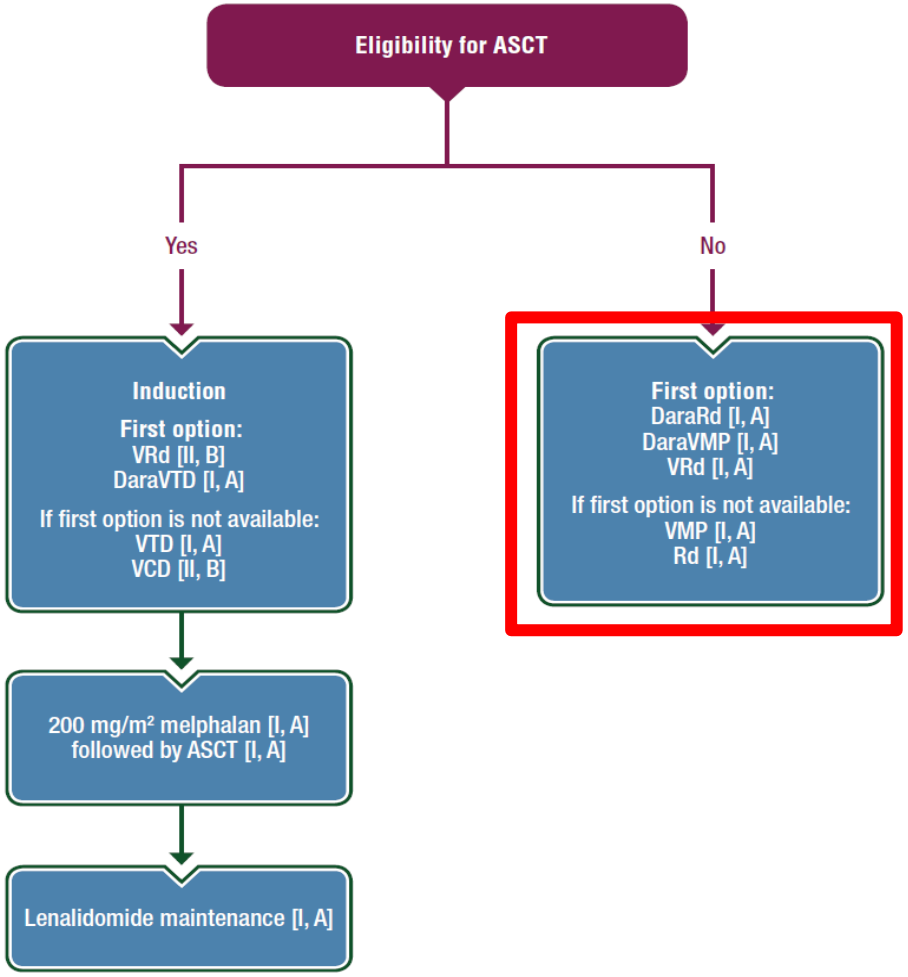
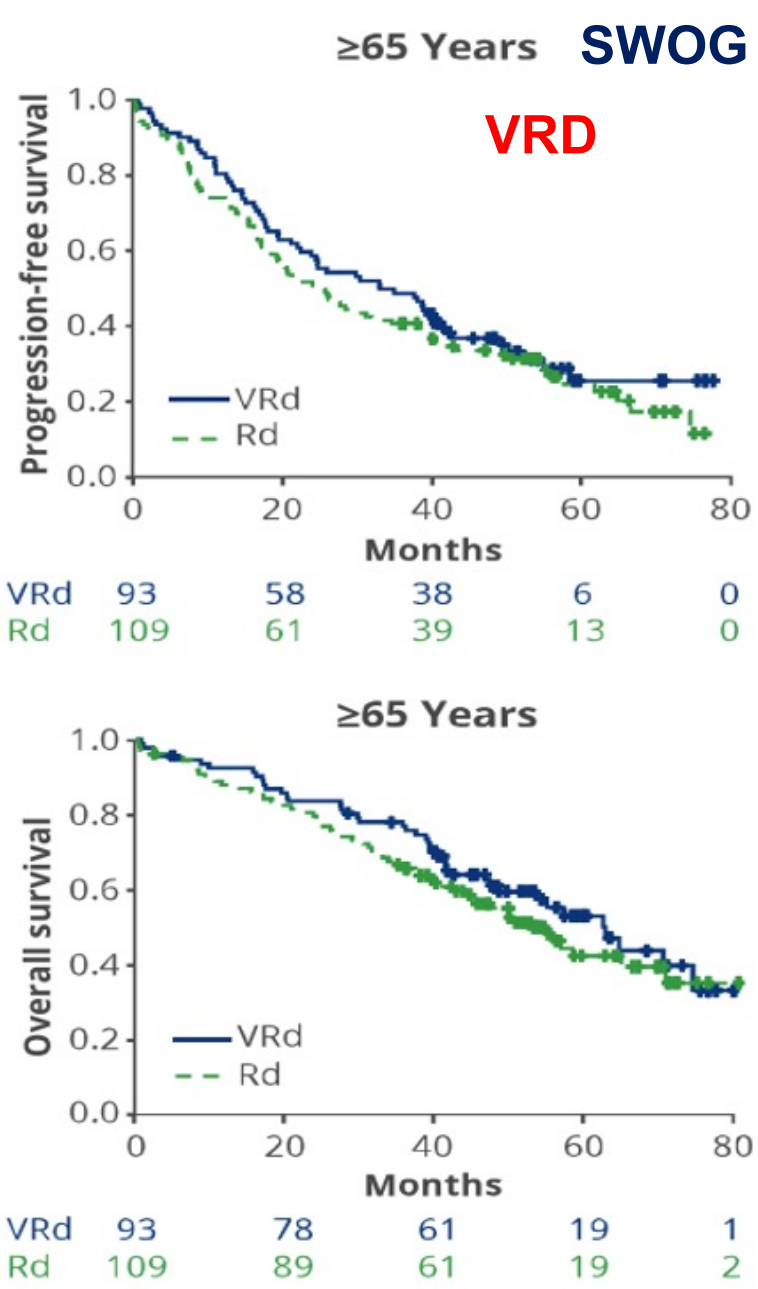
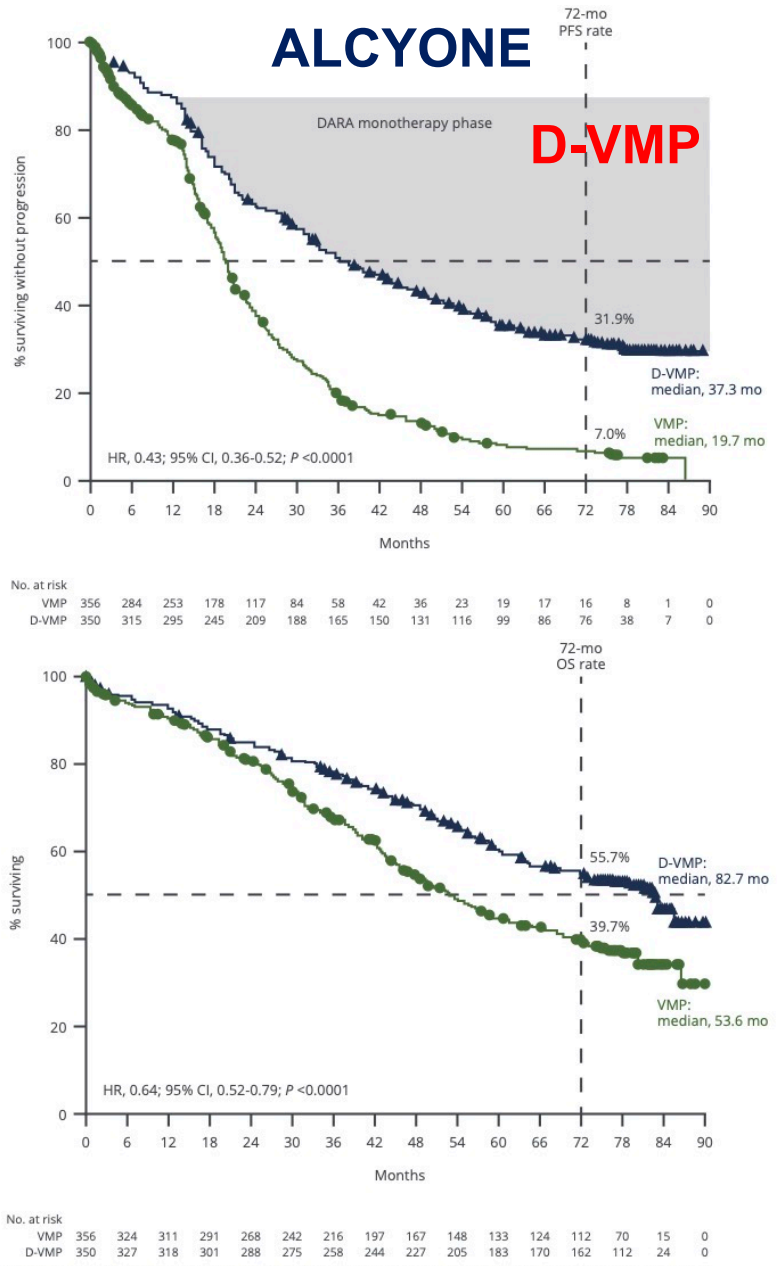


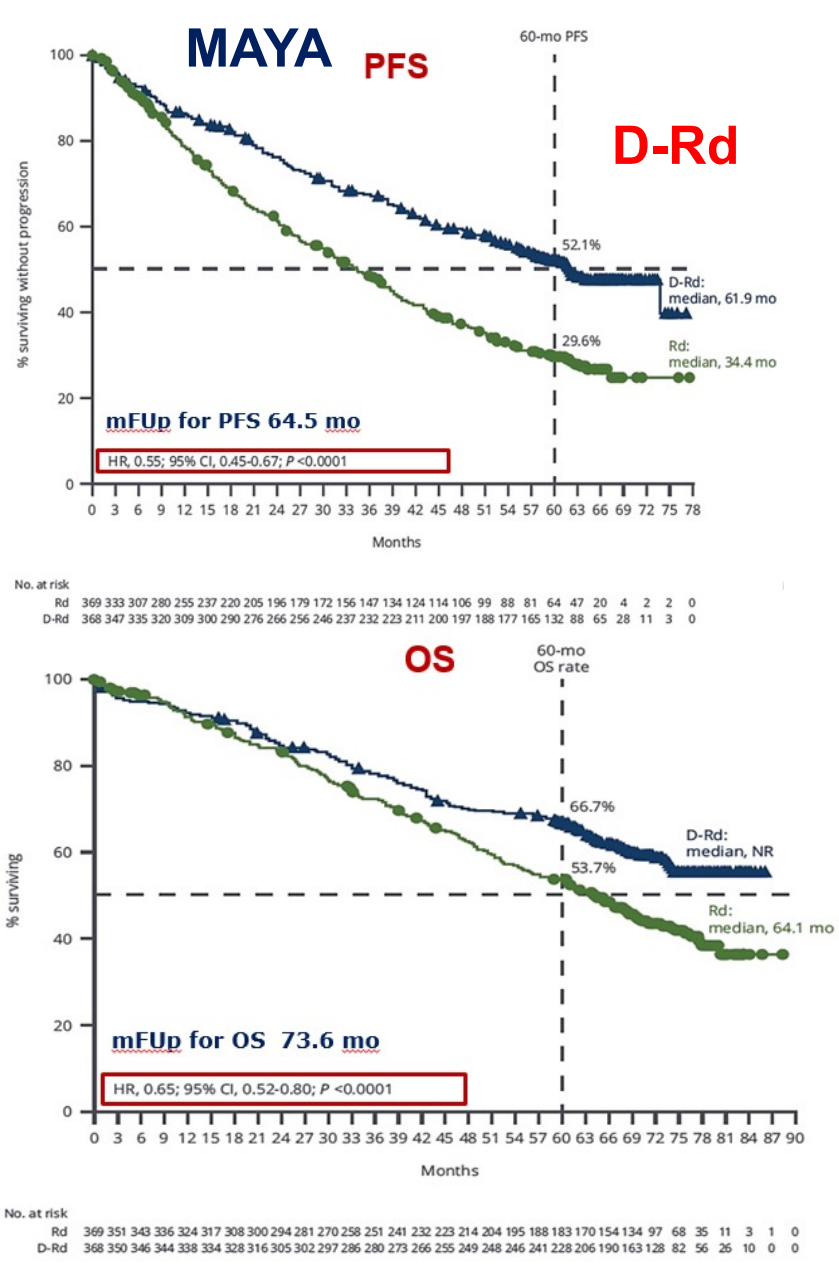
Treatment endpoints

- **To maximize the rate of undetectable MRD**
- **To sustain MRD negativity**
- To prolong PFS/OS, offering a chance of cure (to a fraction of patients)
- To inform clinical decisions and tailor treatment

Upfront treatments for ASCT-ineligible NDMM patients







Durie B et al. ASH2022:4497; Mateos MV et al. ASH 2022;abstract 4561 (poster presentation); Shaji K Kumar, MD – Poster 4559 ASH 2022

High attrition rates with every new LOT

Patients reaching each LOT (N=4997; EU)[1]

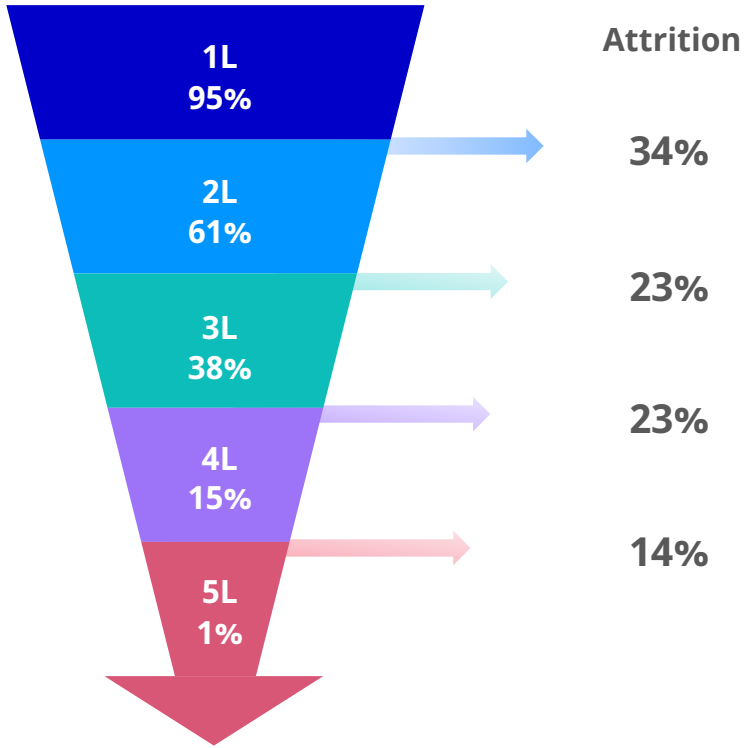
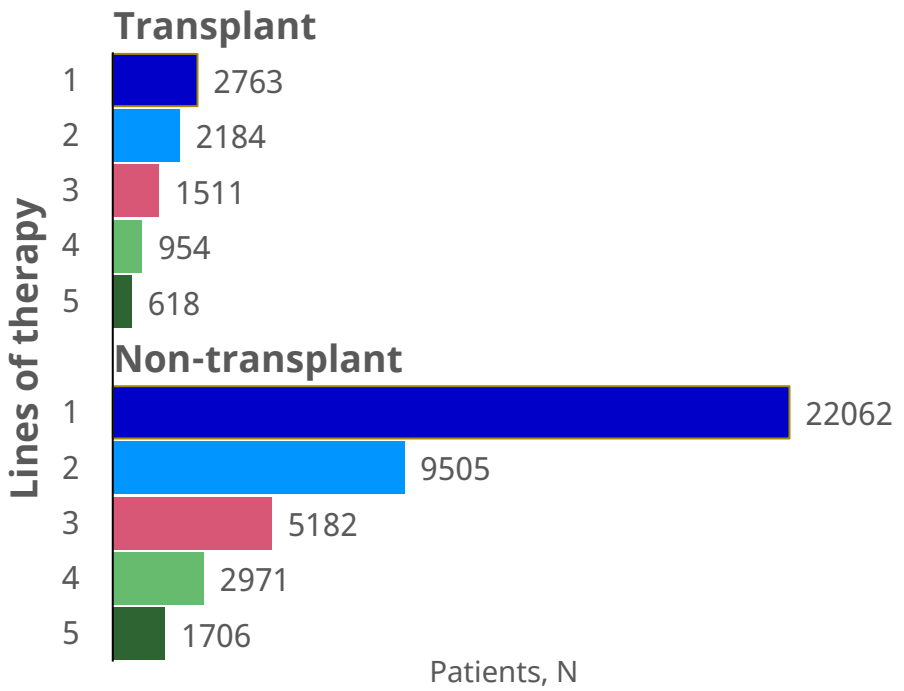


Figure adapted from: Yong K, et al. *Br J Haematol.* 2016;175(2):252-264.[1]

Patients reaching each LOT (US)[2]



Attrition, %
-
21.0
30.8
36.9
35.2
-
56.9
45.5
42.7
42.6

Figure adapted from: Fonseca R, et al. *BMC Cancer.* 2020;20:1087.[2]

With every new LOT, ~15–57% of patients are lost[1,2]

Choose the best available treatment option(s) upfront and in earlines lines

EU, Europe; US, United States; L, line; LOT, line of therapy.

1. Yong K, et al. *Br J Haematol.* 2016;175(2):252-264. 2. Fonseca R, et al. *BMC Cancer.* 2020;20(1):1087.

EHA-ESMO/IMWG clinical practice guidelines 2021: Treatment at first relapse

EHA-ESMO

Second-line options after VRd

- **Lenalidomide sensitive**
  - KRd[c] [I, A]
  - DaraRd[c] [I, A]
  - EloRd[c] [I, A]
  - PomVd[c] [I, A]
  - DaraKd[c] [I, A]
  - IsaKd[c] [I, A]
  - IxaRd[c] [I, A]
  - SVd[c] [I, A]
- **Lenalidomide refractory**
  - PomVd[c] [I, A]
  - DaraKd[c] [I, A]
  - IsaKd[c] [I, A]
  - SVd[c] [I, A]
- **Bortezomib sensitive**
  - KRd[c] [I, A]
  - DaraRd[c] [I, A]
  - EloRd[c] [I, A]
  - PomVd[c] [I, A]
  - DaraKd[c] [I, A]
  - DaraVd[c] [I, A]
  - IsaKd[c] [I, A]
  - SVd[c] [I, A]
  - VenVd[d,e] [I, A}
- **Lenalidomide and bortezomib refractory**
  - DaraKd[c] [I, A]
  - IsaKd[c] [I, A]

Figure adapted from Dimopoulos MA, et al. *Ann Oncol.* 2021;32(3):309-322.[12]

Second-line options after DaraRd[a,b]

- **Lenalidomide sensitive**
  - PomVd[c]
  - Kd[c]
  - EloRd[c]
  - KRd[c]
  - IxaRd[c]
  - SVd[c]
  - VenVd[d,e]
- **Lenalidomide refractory**
  - PomVd[c]
  - Kd[c]
  - SVd[c]
  - VenVd[d,e]

Second-line options after DaraVMP[a,b] or DaraVTd[a,b]

- **Bortezomib sensitive**
  - EloRd[c]
  - KRd[c]
  - IxaRd[c]
  - VRd[c]
  - SVd[c]
  - Kd[c]
  - VenVd[d,e]
- **Bortezomib refractory**
  - EloRd[c]

Figure adapted from Dimopoulos MA, et al. *Ann Oncol.* 2021;32(3):309-322.[12]

IMWG

First relapse[f]

- **Not refractory to lenalidomide**
  - Preferred options[h]: DaraRd[g] or KRd[g]
  - Alternatives[i]: DaraVd,[g] Kd,[g] DaraKd,[g] IsaKd,[g] IxaRd,[g] EloRd,[g] PomVd,[g] SVd[g] (subject to approval)
    When Dara, Isa, K not available: Rd,[g] Vd,[g] VTd,[g] VCD,[g] VMP[g]
- **Refractory to lenalidomide**
  - Preferred options[h]: PomVd[g] DaraKd[g] IsaKd[g]
  - Alternatives[i]: DaraVd,[g] Kd[g]
    Other options[j]: KPd,[d] DaraPd,[d] IxaPd[d]
    When Dara, Isa, K or Pom not available: VCD,[g] Vd,[g] VMP[g]

Figure adapted from Moreau P, et al. *Lancet Oncol.* 2021;22(3):e105-e118.[13]

This slide may include drugs which are not yet approved in your country.

[a]Patients who progress while on monthly Dara are considered as Dara-refractory. [b]All recommendations for patients who receive front-line therapy with Dara-based therapies are based on panel consensus as there are no trials evaluating regimens in second-line therapy that include patients refractory or exposed to Dara. [c]VRd, DaraVTd, DaraRd, DaraVMP, VMP, RD, KRd, DaraRd, EloRd, PomVd, DaraKd, IsaKd, IxaRd, PomVd, KRd, EloRd, PomVd, DaraVd, Kd, IsaPomd, EloPomd, DaraPomd, EloPomd, DaraVd, SVd, PomCd, Dara, Sd, and belantamab mafodotin are approved by EHA for MM.[1-11] [d]**Not approved by EHA for MM**. [e]Patients with t(11;14). [f]Consider salvage auto-transplantation in eligible patients. [g]Approved by the EMA for MM.[1-11]. [h]Grade of recommendation: 1A. [i]Grade of recommendation: 1B. [j]Grade of recommendation: 1C. ASCT, autologous stem cell transplant; BCL-2, B-cell lymphoma 2; C, cyclophosphamide; cd, cluster of differentiation; d, dexamethasone; Dara, daratumumab; EHA, European Hematology Association; Elo, elotuzumab; ESMO, European Society for Medical Oncology; IMiD, immunomodulatory imide drug; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; M, melphalan; MAb, monoclonal antibody; MM, multiple myeloma; P, prednisone; PI, proteasome inhibitor; Pom, pomalidomide; R, lenalidomide; S, Selinexor; T, thalidomide; V, bortezomib.

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Second-line treatment options[a]

	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$^{10\text{-}5}$ 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**

This table may include drugs which are not yet approved in your country.

[a]The table on this slide includes data from various trials. Direct comparisons should not be made as various factors (such as patient populations) differ among trials.

1PLoT, 1 prior line of therapy; CD, cluster of differentiation; CR, complete response; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; HR, hazard ratio; Isa, isatuximab; ITT, intent to treat; Ixa, ixazomib; K, carfilzomib; Len-refr, lenalidomide-refractory; LOTs, lines of therapy; mPFS, median PFS; MRD, measurable residual disease; NA, not available; NC, not calculable; NGS, next generation sequencing; NR, not reached; P, pomalidomide; R, lenalidomide; V, bortezomib.

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).

EHA-ESMO/IMWG clinical practice guidelines 2021: Treatment at first relapse

EHA-ESMO

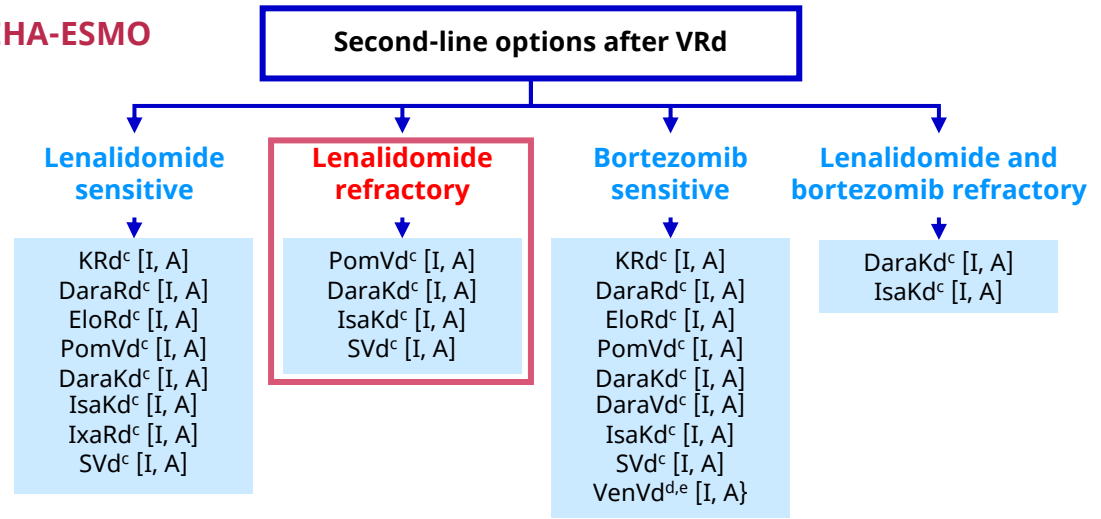
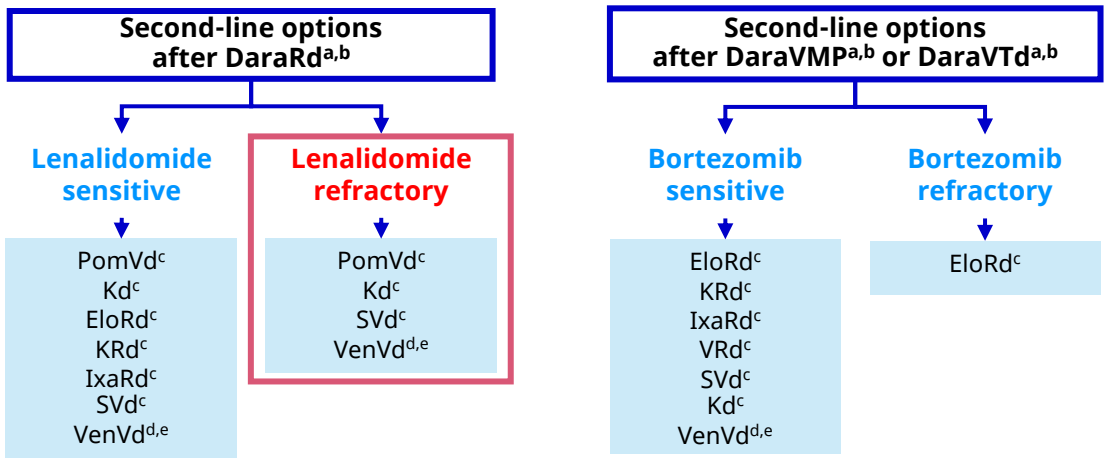


Figure adapted from Dimopoulos MA, et al. *Ann Oncol.* 2021;32(3):309-322.[12]



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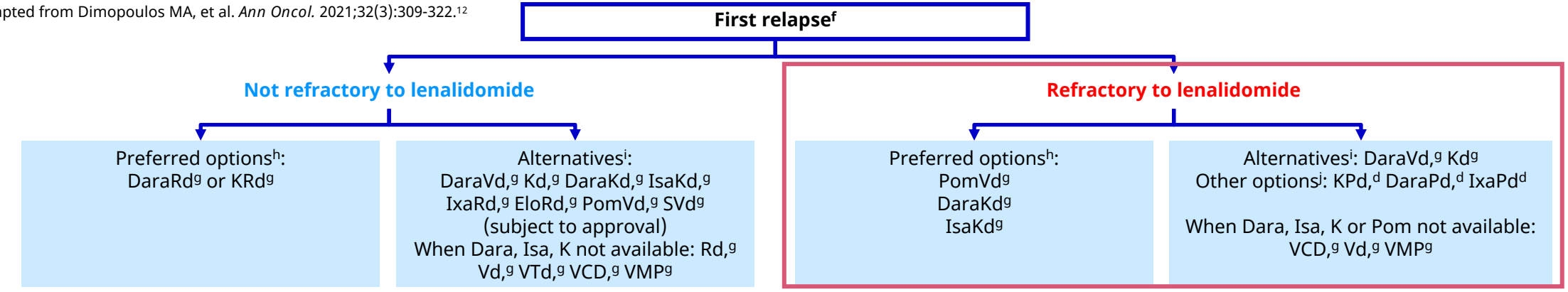
IMWG



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Kd
Kd-Isa
P-Vd
Pd-D
Vd-D

Second-line treatment options[a]

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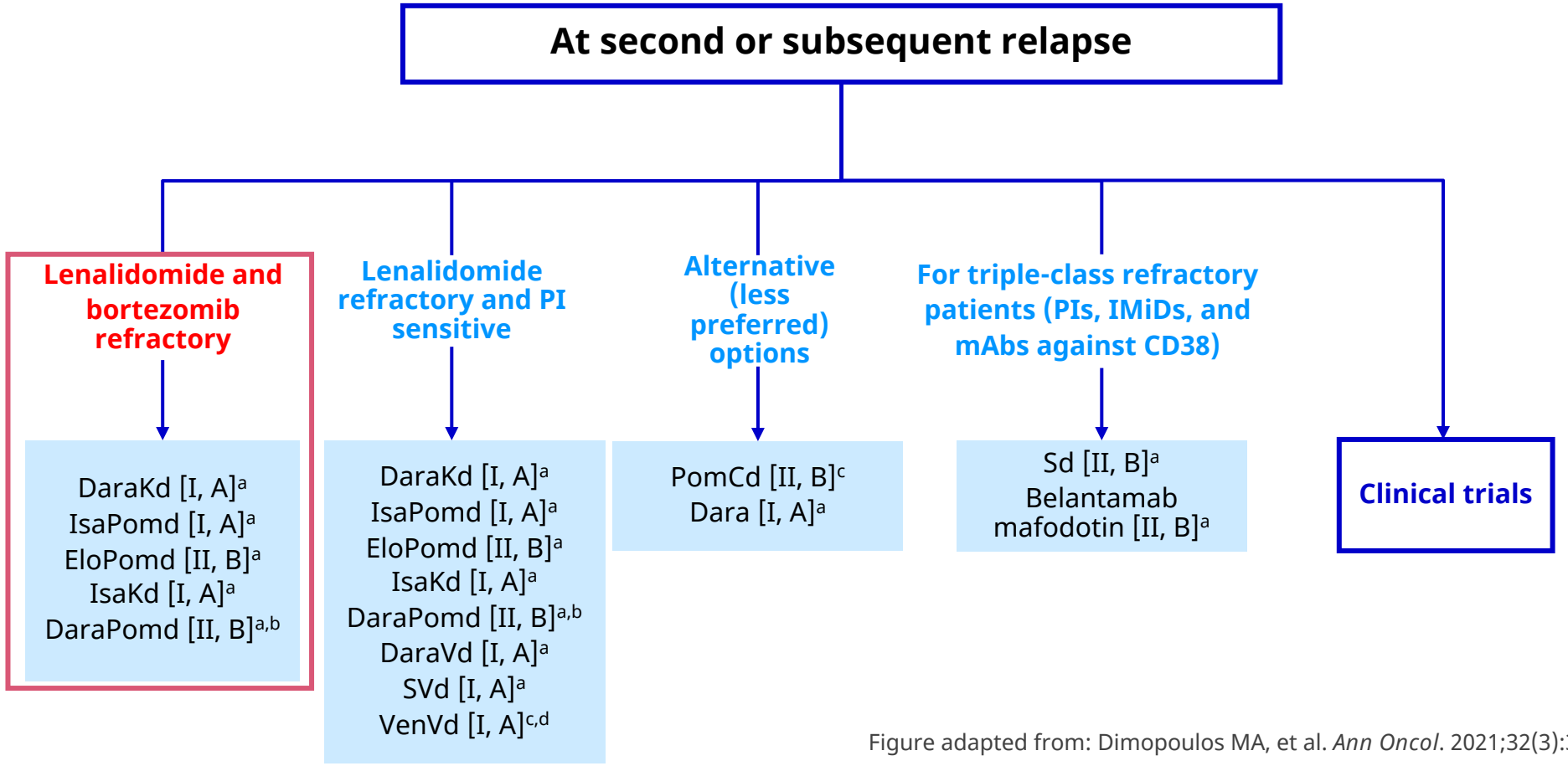
EHA-ESMO clinical practice guidelines 2021: Treatment at second relapse



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[a]Approved by EMA for MM.[2-7] [b]Only phase IB data are published for DaraPomd. Publication of phase 3 data are expected in 2021. [c]**Not approved by EMA for MM.** [d]For patients with t(11;14) or high BCL2 levels.
C, cylophosphmide; CD, cluster of differentiation; Dara, daratumumab; d, dexamethasone; Elo, elotuzumab; IMiD, immunomodulatory drug; Isa, isatuximab; K, carfilzomib; mAb, monoclonal antibody; MM, multiple myeloma; Pom, pomalidomide; PI, proteasome inhibitor; S, selinexor; V, bortezomib; Ven, venetoclax.

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Phase 2 and 3 studies of Pd-based triplets[a]

Pd-Dara
Pd-Isa
Pd-Elo
Kd-Isa

	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

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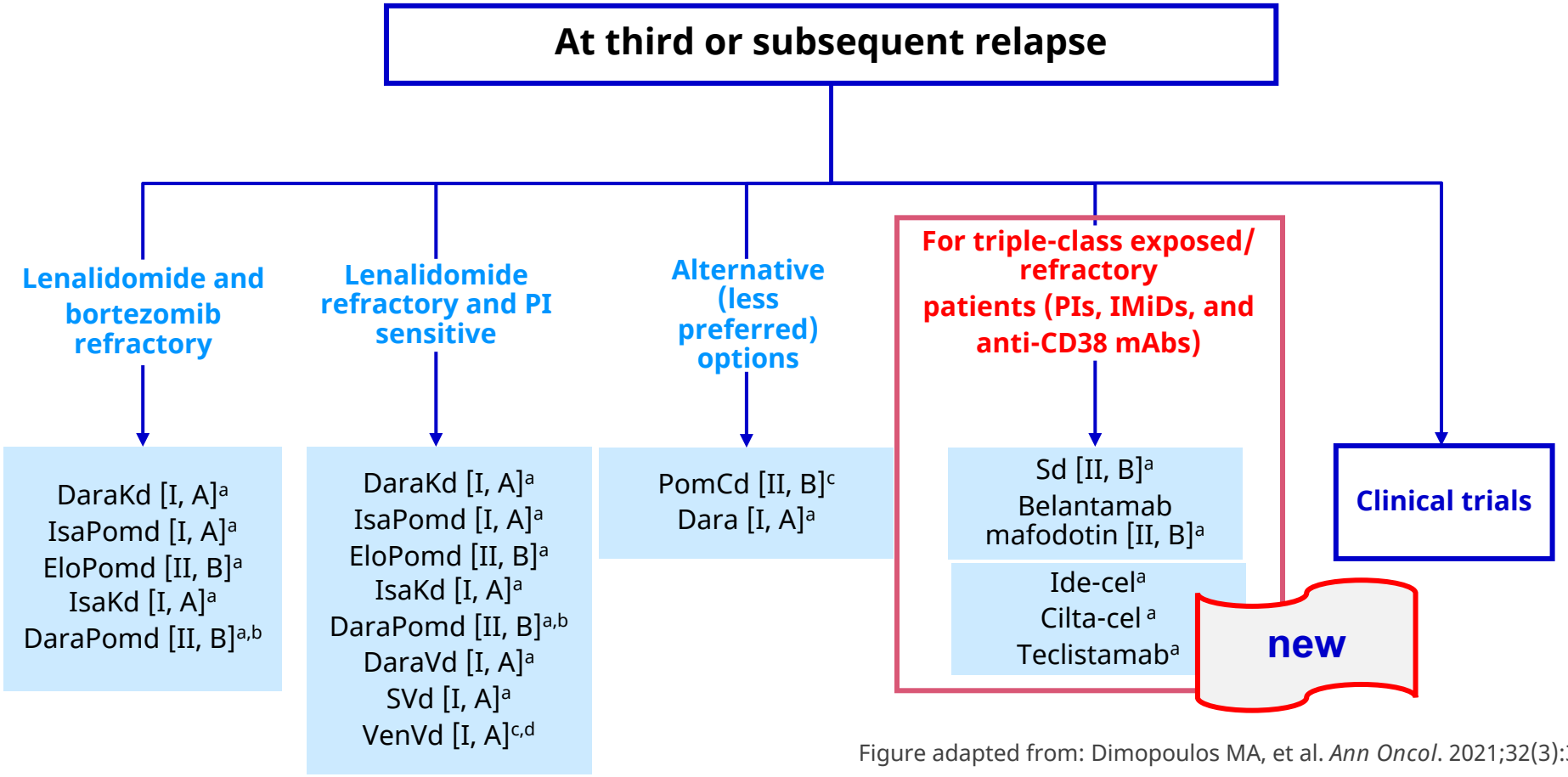
[b]Ref to len at last line, n=93 (60%); n=88 (58%). [c]PI and IMiD refractory patients, median follow-up 16.9 months.

AE, adverse event; CI, confidence interval; d, dexamethasone; D, daratumumab; Elo, elotuzumab; Isa, isatuximab; IQR, interquartile range; len, lenalidomide; MRD, measurable residual disease; NA: not available; ORR, overall response rate; P, pomalidomide; PFS, progression-free survival; ref, refractory; V, bortezomib; VGPR, very good partial response.

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).

EHA-ESMO clinical practice guidelines 2021: Treatment at third or subsequent relapse



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[a]Approved by EMA for MM.[2-7] [b]Only phase IB data are published for DaraPomd. Publication of phase 3 data are expected in 2021. [c]**Not approved by EMA for MM.** [d]For patients with t(11;14) or high BCL2 levels.
C, cylophosphmide; CD, cluster of differentiation; Dara, daratumumab; d, dexamethasone; Elo, elotuzumab; IMiD, immunomodulatory drug; Isa, isatuximab; K, carfilzomib; mAb, monoclonal antibody; MM, multiple myeloma; Pom, pomalidomide; PI, proteasome inhibitor; S, selinexor; V, bortezomib; Ven, venetoclax.

1. Dimopouplos MA, et al. *Ann Oncol.* 2021;32(3):309-322. 2. Carfilzomib Summary of Product Characteristics, 2021. https://www.ema.europa.eu/en/documents/product-information/kyprolis-epar-product-information_en.pdf. Accessed October 4, 2022. 3. Isatuximab Summary of Product Characteristics, 2022. https://www.ema.europa.eu/en/documents/product-information/sarclisa-epar-product-information_en.pdf. Accessed October 4, 2022. 4. Elotuzumab Summary of Product Characteristics, 2019.https://www.ema.europa.eu/documents/product-information/empliciti-epar-product-information_en.pdf. Accessed October 4, 2022. 5. Daratumumab Summary of Product Characteristics, 2022. https://www.ema.europa.eu/documents/product-information/darzalex-epar-product-information_en.pdf. Accessed October 4, 2022. 6. Selinexor Summary of Product Characteristics, 2022. https://www.ema.europa.eu/documents/product-information/nexpovio-epar-product-information_en.pdf. Accessed October 4, 2022. 7. Belantamab mafodotin Summary of Product Characteristics, 2022. https://www.ema.europa.eu/documents/product-information/blenrep-epar-product-information_en.pdf. Accessed October 4, 2022.

Strategies to enhance the immune system

Targeting surface antigens with **monoclonal antibodies and ADCs**

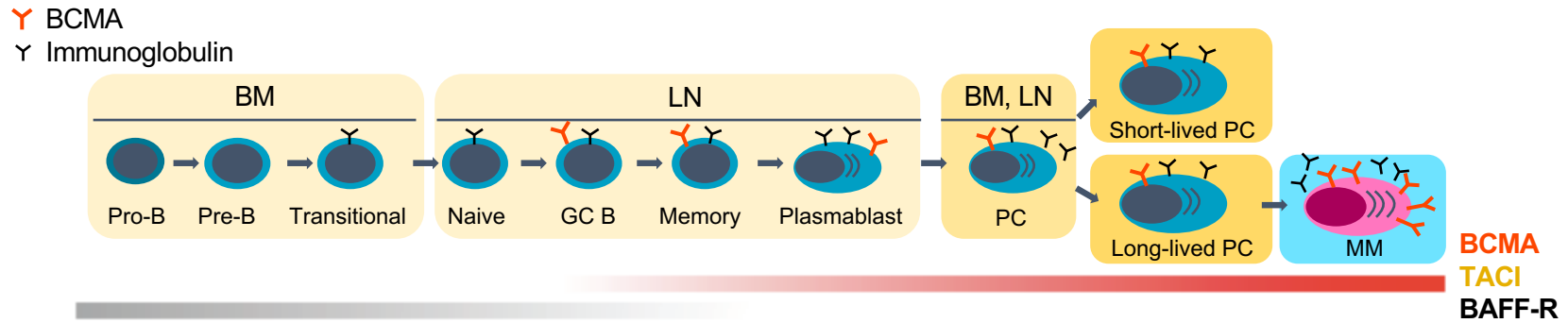
Reversing the immune tolerance with **checkpoint inhibitors**

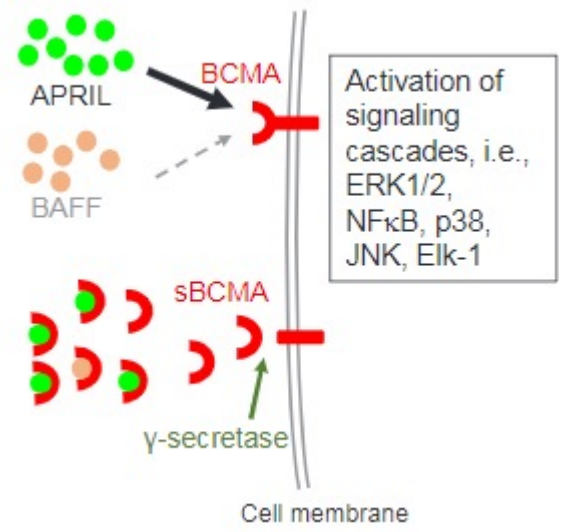
Boosting and redirecting immune effector cells: **CAR-T cells and bispeficific mAbs**

Activating tumour-specific immunity by **vaccines**

Rodríguez Otero P, et al. Haematologica. *2017;102:423-32* **(modified)**.

BCMA: a leading target for ADCs, bispecific antibodies and CAR T





- BCMA is a transmembrane glycoprotein expressed specifically by mature B cells, normal and malignant PCs[1,2]
  - Higher expression in MM cells than normal PCs[1,2]
  - Member of TNFR superfamily
  - Encoded by a gene located on chromosome 16
  - Cleaved from cell surface by γ secretase and released as sBCMA
  - Upon binding with its ligands BAFF and APRIL[1,2] plays a key role in B-cell maturation and differentiation to PCs[1]
  - Promotes myeloma cell growth, chemoresistance, and immunosuppression in the BM microenvironment[1]
- BCMA expression increases as the disease progresses from MGUS to advanced MM[3]

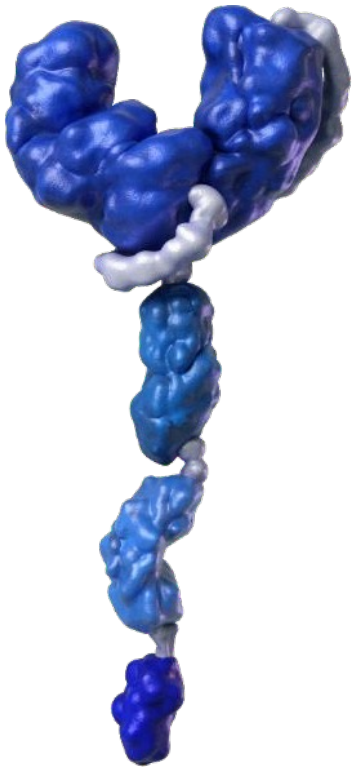
Figures adapted from Cho SF, et al. *Front Immunol*. 2018;9:1821.

APRIL, a proliferation-inducing ligand; BAFF-R, B-cell activating factor receptor; BCMA, B-cell maturation antigen; BM, bone marrow; ERK1/2, extracellular signal-regulated protein kinase 1/2; Elk1, E twenty-six like-1; GC, germinal centre; JNK, c-Jun N-terminal kinase; LN, lymph node; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; NF-κB, nuclear factor kappa B; PC, plasma cell; sBCMA, soluble B-cell maturation antigen; TACI, transmembrane activator and CAML interactor; TNFR, tumor necrosis factor receptor.

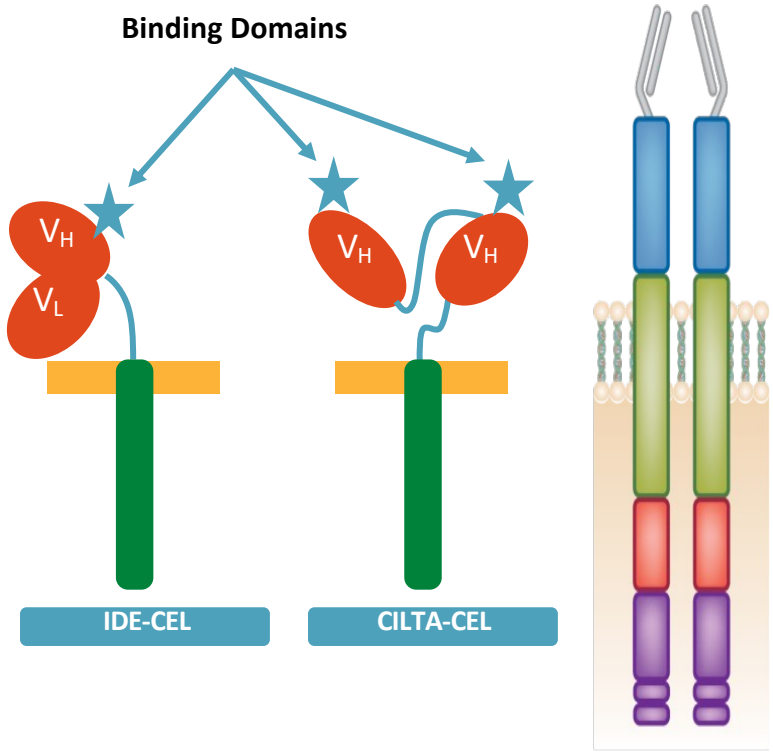
1. Cho SF, et al. *Front Immunol*. 2018;9:1821. 2. Moreaux J, et al. *Blood*. 2004;103(8):3148-3157. 3. Sanchez E, et al. *Br J Haematol*. 2012;158(6):727-738.

CAR-T: structure and functions

Ide-cel



Cilta-cel



-**Extracellular domain** that binds specifically to a target molecule expressed on the tumor cell surface:

-**Single-chain variable fragment** (scFv) **consisting of a heavy and light chain variable region derived fom an anti-BCMA mAb**

-Recognize tumor-associated antigens in a non-MHC-specific manner

-**Transmembrane hinge region** derived from CD8 provides flexibility to allow reorientation to bind antigen

-**Intracellular costimulatory domain (II and III generation CAR-T)**: CD28 or 4-1BB (more robust cytokine production and enhanced cytolytic activity of CAR-Ts)

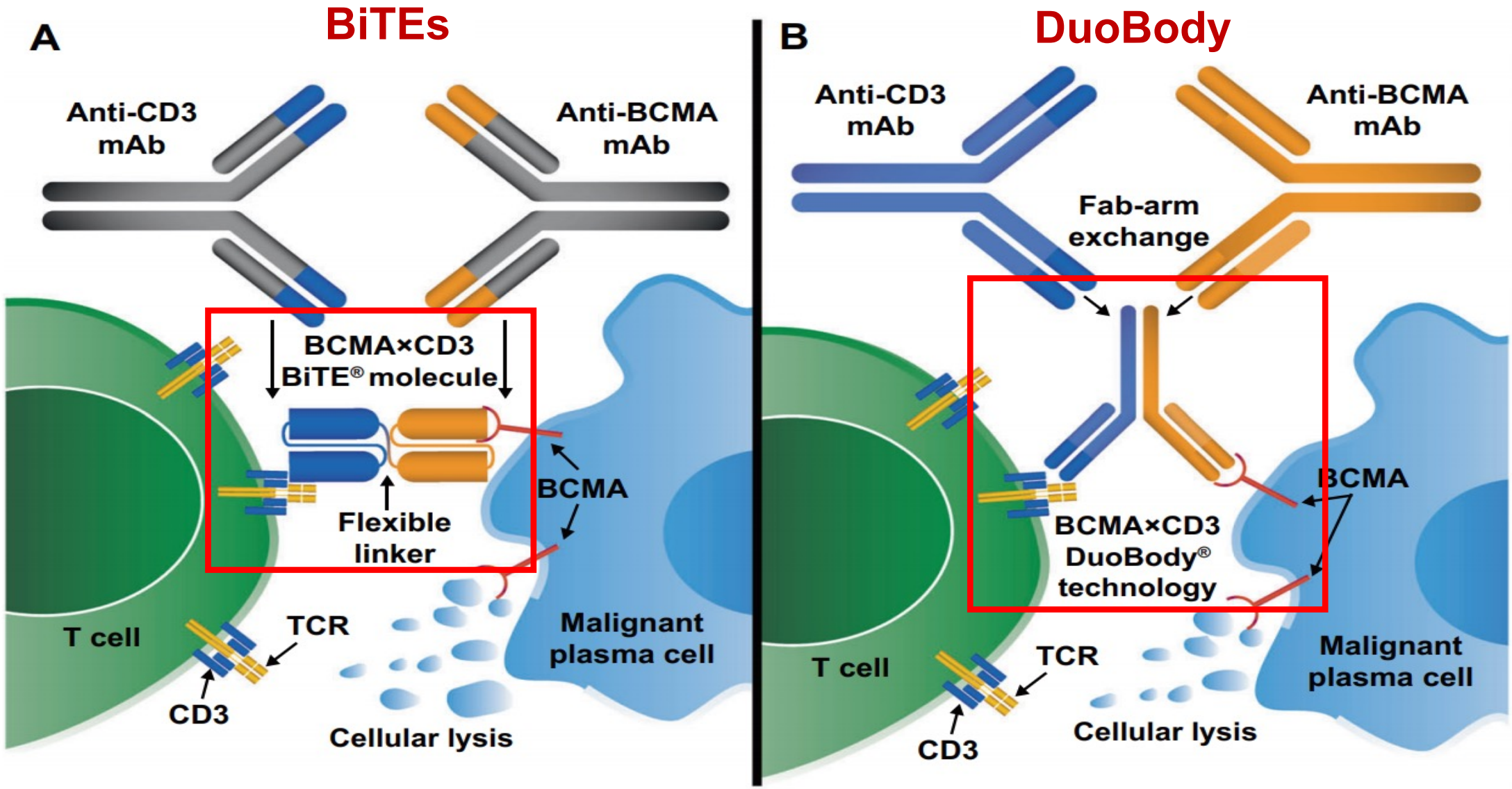
-**Intracellular T-cell activation domain**: CD3ζ

- **Antigen recognition** via extracellular domain and **HLA-independent activation of T cells** with powerful cytotoxic and memory functions via intracellular domain
- **Remodelling of tumor suppressive microenvironment**

Adapted from Kershaw MH et al. Nat rev Cancer 2013

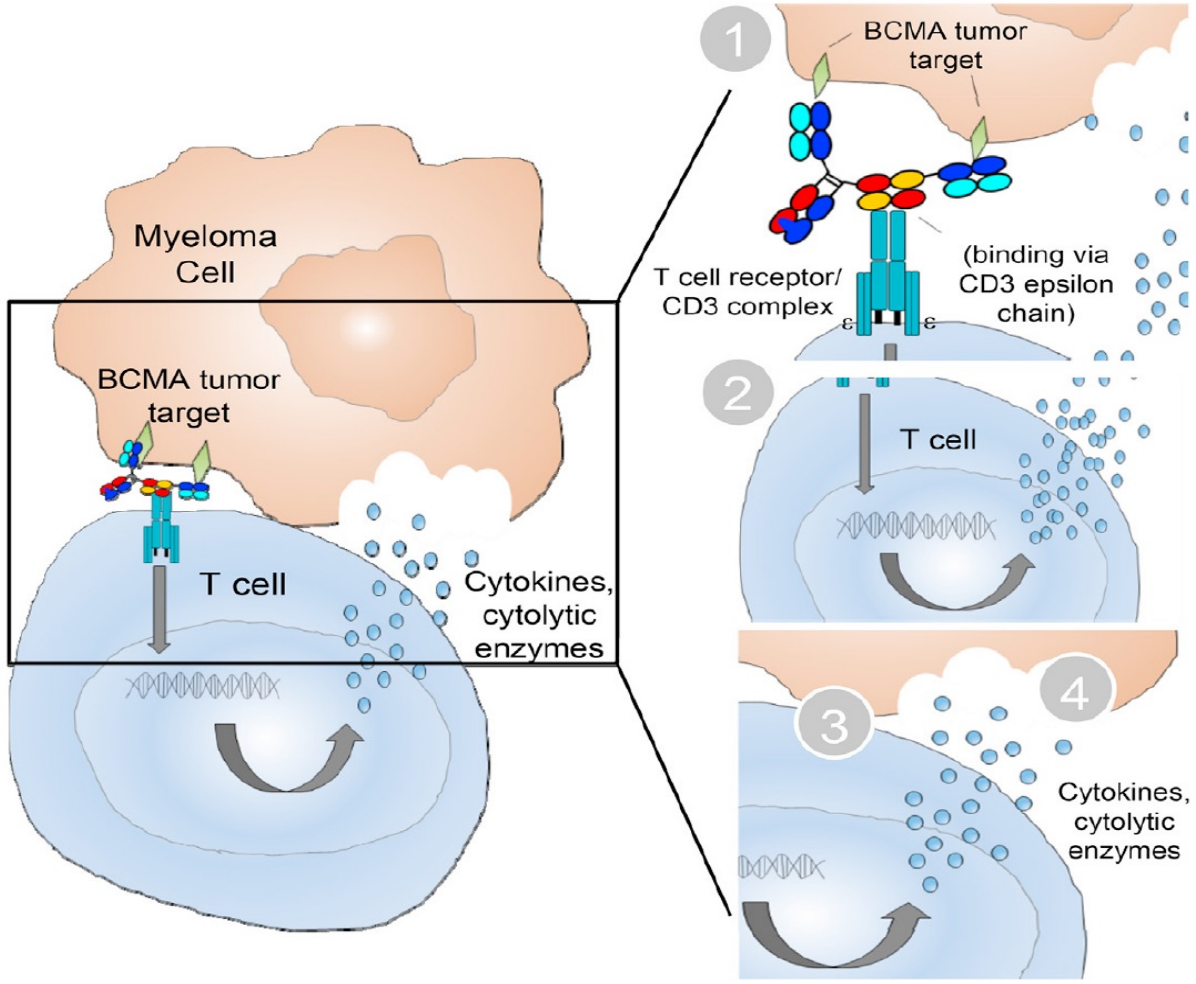
- CAR, chimeric antigen receptor; MHC, major histocompatibility complex; MM, multiple myeloma; NK, natural killer.

Bispecific antibodies: different constructs



Shah N et al. Leukemia 2020

Bispecific antibodies: functions



- Engage tumor cells and cytotoxic immune effector cells **creating an immunologic synapse that leads to T/NK cell activation**[1,2]
- Activated immune effector cells **release perforins and granzymes inducing tumor cell lysis**[2]
- **The Fc receptor** engages the innate immune system and **induces ADCC, ADCP, and CDC**

Figure adapted from Seckinger A, et al. *Cancer Cell.* 2017;31(3):396-410.
BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; NK, natural killer.
1. Zhou X, et al. *J Clin Med.* 2020;9(7):2166. 2. Seckinger A, et al. *Cancer Cell.* 2017;31(3):396-410.

CAR-T cell therapies

	Approved CAR-T cells		Academic	Alternative manufacturing	Human scFv		Allo-CAR	GPRC5D
	Ide-cel KarMMa[1] (n = 128)	Cilta-cel CARTITUDE-1[2] (n = 97)	ARI0002h[3] (n = 30)	P-BCMA-101 PRIME[5] (n = 53)	CT053[6] LUMMICAR (n = 20)	CT103A[7] (n= 79)	ALLO-715 UNIVERSAL[8] (n = 43)	MCARH10[9] (n= 17)
Phase	II	Ib/II	I/II	I/II	I	I/II	I	I
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D
scFv	Chimeric mouse	Chimeric llama	Humanized	Chimeric mouse	Human	Human	Human	Human
Co-stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB
Specificity	Autologous	Autologous	Autologous	Autologous - piggyBac	Autologous	Autologous	Allogenic CD52 & TCR KO	Autologous
Age, (range)	61 (33-78)	61 (56-68)	61 (36-74)	60 (42-74)	62 (33-76)	56 (39-70)	64 (46-77)	60 (38-76)
# of lines	6	6	4	8	NA	5	5	6
HR cytog, %	35	24	36	NA	NA	35	48	77
EMD, %	39	13	20	NA	NA	NA	21	41
Triple-R, %	84	88	61	60	NA	17	91	94

*There are no head-to-head comparisons of these data and naïve comparison should be conducted with caution

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; EMD, extramedullary disease; HR cytog, high-risk cytogenetics; NA, not available; ScFv, single-chain variable fragment; TCR, T-cell receptor; triple-R, triple-class refractory

1. Munshi N et al. N Eng J Med 2021;384:705-16; 2. Berdeja J et al. Lancet 2021;398;314-24; 3. Fernández de Larrea C, et al. ASH 2021;abstract 2837; 4. Raje N et al. ASH 2021 abstract 548; 5. Costello C, et al. ASH 2020;abstract 134; 6. Kumar S, et al. ASH 2020; 7. Li C, et al. ASH 2021;abstract 143; 8. Mailankody S, et al. ASH 2021;abstract 615; 9. Mailankody S, et al. ASH 2021;abstract 827

T-cell redirecting bispecific antibodies in MM

	Teclistamab[1] (n=165)	AMG701[2] (n=85)	REGN5458[3] (n=49)	TNB-383B[4] (n=58)	CC-93269[5] (n=30)	Elranatamab[6] (n=94)	Talquetamab[7] (n=82)	Cevostamab[8] (n=53)
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	FcRH5
Administration	SC, QW	IV, QW	IV, QW then Q2W	IV, Q3W	IV, QW then Q2W	SC, QW then Q2W	SC, QW/Q2W 405/800 µg/kg	IV, Q3W
Median prior LoT	5 (2-14)	6 (2-25)	5 (2-17)	6 (3-15)	5 (3-13)	5 (2-12)	6 (2-17)/5 (2-17)	6 (2-15)
Triple refractory	77.6%	62%	100%	64%	67%	96%	76%/77%	72%
CRS, G≥3	72%, 0.6%	64%, 9%	38%, 0%	69%, 3%	77%, 3%	59%, 0%	76%, 1%/79%, 0	76%, 2%
Neurotoxicity, G≥3	14.5%, 0.6%	NR	12%, 0	NR	NR	2%, 0%	NR	28%, 0
ORR	63%	26%	51%	50.7%	89% at 6-10 mg	66% at RP2D	70%/64%	53%
CR	CR 7%	17% ≥VGPR	43% ≥VGPR	43% ≥CR	44% at 6-10 mg	30%	7%/11.4%	18%
MRD – (10^{-5})	44 out of 54	6 out of 7	4 out of 10	NR	12 out of 13	3 patients	NR	6 out of 7

*There are no head-to-head comparisons of these data and naïve comparison should be conducted with caution
BCMA, B-cell maturation antigen; CR, complete response; CRS, cytokine release syndrome; IV, intravenous; LoT, lines of treatment; NR, not reported; RP2D, recommended phase 2 dose; SC, subcutaneous; MRD, minimal residual disease; NT, neurotoxicity; ORR, overall response rate; QW, weekly, Q2W/Q3W, every 2/3 weeks; VGPR, very good partial response

[1]Nooka A et al. ASCO 2022;abstract 8007; [2]Harrison S et al. ASH 2020;abstract 181; [3]Zonder J, et al. COMy 2022;abstract only; [4]Kumar S et al. ASH 2021;abstract 900; [5]Costa L et al. ASH 2019;abstract 143; [6]Bahlis N et al. ASCO 2021;abstract 8006; [7]Minnema M et al. ASCO 2022;abstract 8015; [8]Cohen A et al. ASH 2020;abstract 292

Immunotherapies: advantages/disadvantages

	Antibody–drug conjugate	CAR T-cells	Bispecific antibody
Advantages	Off-the-shelf	Personalized	Off the shelf
	Targeted cytotoxicity Not dependent on T-cell health	Targeted immuno-cytotoxicity with rapid and deep responses	Targeted immuno-cytotoxicity
	No lymphodepletion No steroids	Single infusion (“one and done”)	No lymphodepletion Minimal steroids
	Available to any infusion center Outpatient administration	Potentially persistent	Likely available for local administration
Disadvantages		Fact accredited center required (hospitalization likely required)	Initial hospitalization required
	Currently requires REMS/Ophtho	CRS and Neurotoxicity; requires ICU and Neurology services	CRS and Neurotoxicity possible
	Currently Requires dose adjustments and holds	Dependent on T-cell health (manufacturing failures)	Dependent on T-cell health (T-cell exhaustion)
	Requires continuous administration	Requires significant support social – caregiver required	Requires continuous administration
	$$	$$$$ - Cure possible?	$$$ - functional cure?

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICU, intensive care unit; REMS, risk evaluation mitigation strategies

Courtesy of Dr. T. Martin

Tailoring and sequencing immunotherapies

Selection of immunotherapy

ADCs
Bispecific antibodies
CAR T
New CARs/dual CAR
NK or T or both
Better constructs
New manufacturing (rapid)

Selection of targets
BCMA
GPRC5D
FcRH5
Other antigen targets

Optimal selection of patients

Who will benefit the most from each of these strategies? Earlier treatment lines? (upfront?), lower tumor burden?, which cytogenetic risk?

Combined with each other?
Administered sequentially?

Rodríguez-Lobato LG et al. Front Oncol. 2020;10:1243

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; NK, natural killer; ScFv, single-chain variable fragment

blood

CLINICAL TRIALS AND OBSERVATIONS

Comment on Rajkumar et al, page 4050

Myeloma therapy: the future is bright

Michele Cavo UNIVERSITY OF BOLOGNA

In a phase 2 study of lenalidomide combined with dexamethasone as front-line therapy for multiple myeloma, Rajkumar and colleagues report an excellent rate of responses, including 38% complete remission or near complete remission.