La rivoluzione terapeutica nel **linfoma** e nel **mieloma**

Napoli, Royal Hotel Continental • 14–15 Maggio 2026

Nuove linee guida EHA-EMN: quali novità?

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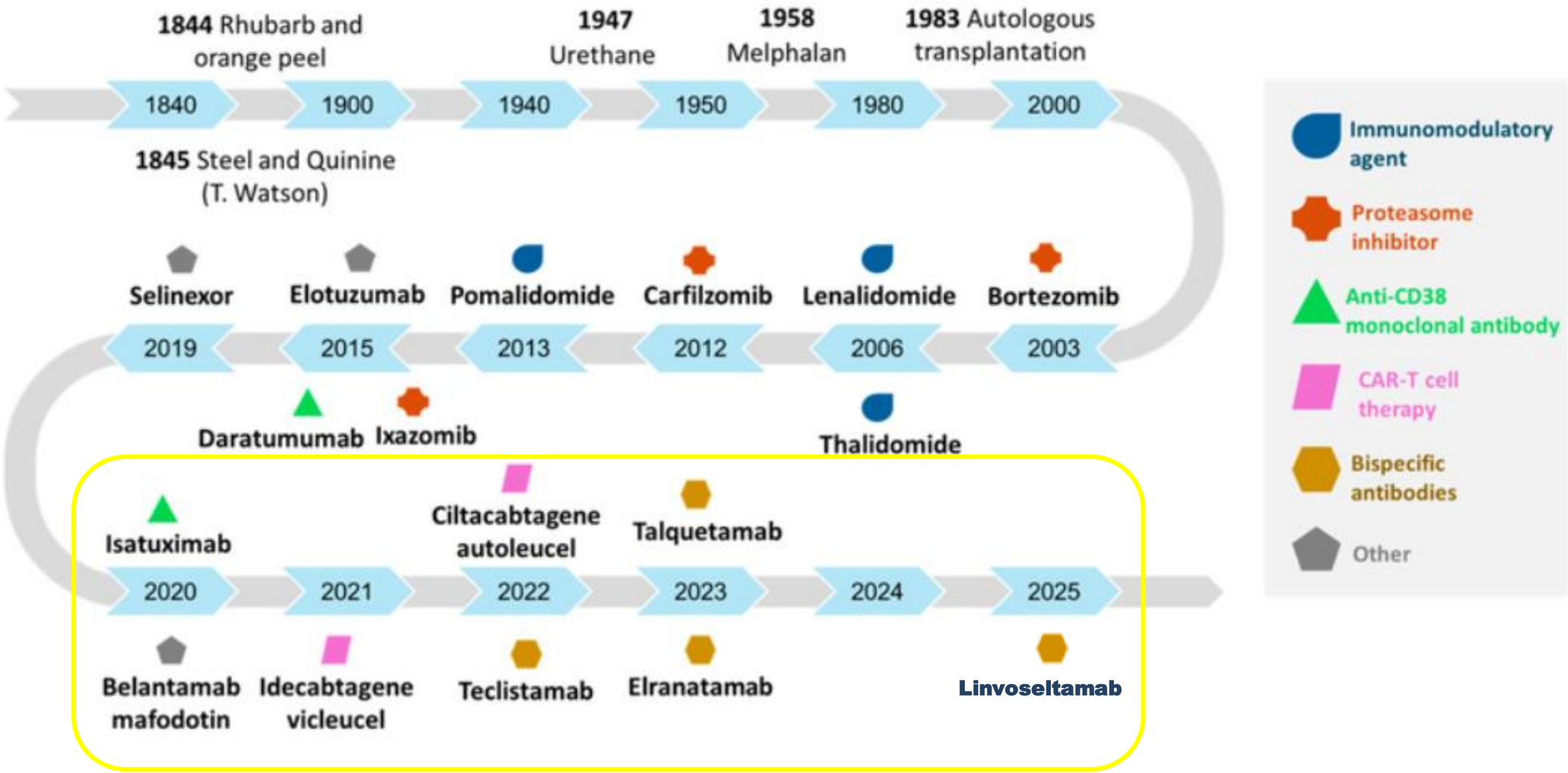
Disclosures

Nothing to declare

Evolving landscape in Multiple Myeloma



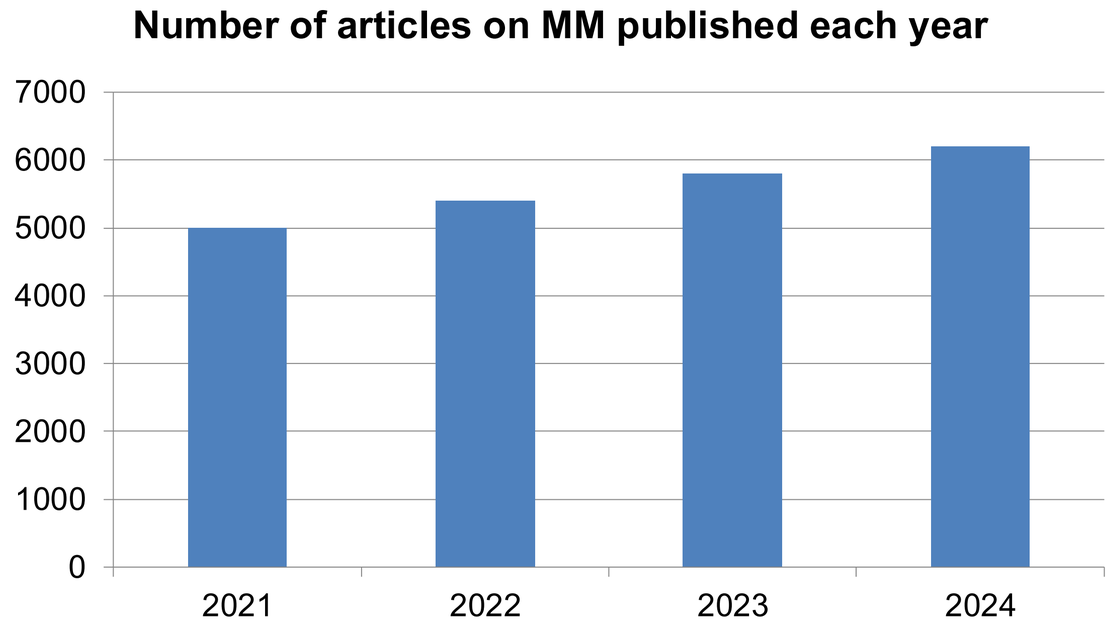
Besliu et al. Cancers 2025, 17, 525

- A **significant number of interventional trials for MM** were active or initiated **between 2021 and 2025:**

Total Interventional Trials: A 2025 analysis covering the previous decade identified a dataset of **1,209 interventional clinical trials** specifically focusing on multiple myeloma therapeutics, which were active or initiated during that period.

Trial Phases: The trials initiated in this period were heavily focused on early intervention and new therapies, with 326 Phase 1 trials, 429 Phase 2 trials, and 127 Phase 3 trials.

- it is estimated that between **22,000 and 25,000 scientific articles** have been written in this five-year period.



Source: ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, International Myeloma Foundation

2021

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†

nature reviews clinical oncology

https://doi.org/10.1038/s41571-025-01041-x

Evidence-based guidelines

Check for updates

2025

EHA–EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma

WHAT'S NEW?

MM guidelines update

- Risk stratification
- Intensity of first-line therapy and use of MRD
- Early use of immunotherapies in relapses
- How to manage old/new toxicities and supportive care

Raccomandation on examinations on diagnosis, at response, during follow up, at relapse

- The diagnostic criteria for MM and SMM defined in the 2021 EHA guidelines remain unchanged

- The 2016 IMWG definitions for response, PD and R/R have not changed

- In 2016 IMWG gave definition for bone marrow MRD negativity (cut off value < 10 -5), that is the definition of the updated guidelines

Dimopoulos MA et al. Nat Rev Clin Oncol, 2025

Raccomandation on examinations on diagnosis, at response, during follow up, at relapse

Tool	Diagnosis	At response	At follow-up	At relapse
Blood tests				
Blood count and blood smear	Obl	Obl	Obl	Obl
Serum electrophoresis and immunofixation	Obl	Obl	Obl	Obl
Serum free light chain	Obl	Obl to confirm sCR	Obl	Obl
Serum immunoglobulin levels	Obl	Obl	Obl	Obl
Renal and liver function tests	Obl	Obl	Obl	Obl
Calcium	Obl	Obl	Obl	Obl
Lactate dehydrogenase	Obl	Obl	Obl	Obl
Albumin, β_2 microglobulin	Obl	NR	Opt	Obl
Flow cytometry	Opt	NR	NR	Opt
Urine tests				
Urine sample from 24-h urine collection to check for proteinuria and serum free light chain proteinuria	Obl	NR	NR	Obl
Urine electrophoresis and immunofixation	Obl	Obl	NR	Obl
Bone marrow assessments				
Bone marrow cytology and biopsy to confirm plasmacytosis and monoclonality	Obl	Obl to confirm CR or for non-secretory MM	NR	Opt (obl for non-secretory MM)
NGF or NGS to detect clonal plasma cells	Obl	Obl to confirm MRD negativity in patients with CR or sCR	Every 12 months in MRD-negative patients	Opt
Cytogenetics: karyotype and FISH for detection of del17p, t(4;14), t(14;16), t (14;20), 1q gain or amplification, del1p32 and t(11;14), and NGS for *TP53* mutations	Obl	NR	NR	Obl in patients with del17p, del1p32, 1q gain or amplification and *TP53* mutations
Advanced techniques: GEP, NGS	Only in clinical trials	Only in clinical trials	Only in clinical trials	Only in clinical trials
Imaging				
PET–CT or DWI MRI	Obl	Obl to confirm imaging MRD	Every 12 months in MRD-negative patients	Obl (also for detection of paramedullary or extramedullary disease)
WBLD CT	Obl (if PET–CT or DWI MRI NA)	NR	When symptomatic (or CT of the symptomatic area)	Obl (if PET–CT or DWI MRI NA)

Urine-based tests are not obligatory for the assessment of response or during follow-up, but should be performed at diagnosis and at each relapse to exclude other pathologies (such as light chain amyloidosis or FLC deposition disease

Both PET–CT and DWI MRI are considered complementary to bone marrow MRD for the evaluation of MRD negativity

Dimopoulos MA et al. Nat Rev Clin Oncol, 2025

Risk stratification

Stage	Criteria	Tumor mass
I	All the following:	Low tumor mass
	Hb > 10 g/dL	< 0.6 x 10^{12}/m^2
	Normal calcium	
	IgG < 5 g/dL; IgA < 3 g/dL	
	Monoclonal urinary protein < 4 g/24h	
	No or single bone lesion	
II	Between Stages I and II	Intermediate tumor mass
III	Any of the following:	High tumor mass
	Hb < 8.5 g/dL	> 1.2 x 10^{12}/m^2
	Calcium < 12 mg/dL	
	IgG > 7 g/dL; IgA > 5 g/dL	
	Monoclonal urinary protein > 12 g/24h	
	Multiple osteolytic lesions, fractures	
Subclass	A – creatinine < 2 mg/dL	
	B – creatinine ≥ 2 mg/dL	

ISS

B2-microglobulin
Albumin

Stage I: Serum β2M <3.5 mg/L and serum albumin ≥3.5 g/dL

Stage II: Not ISS stage I nor III

Stage III: Serum β2M ≥5.5 mg/L

R-ISS

ISS
LDH
Cytogenetic lesions
t(4;14), and/or t(14;16) and/or del17p

Stage I: ISS stage I, t(4;14), and/or t(14;16) and/or del17p negativity by FISH, and normal serum LDH

Stage II: Not ISS stage I nor III

Stage III: ISS stage III and either elevated serum LDH or t(4;14), and/or t(14;16) and/or del17p positivity by FISH

R2-ISS

ISS
LDH
Del(17p),t(4;14),1q+

Additive score:
ISS II: *1 point*
ISS III: *1.5 points*
Del(17p): *1 point*
Elevated serum LDH: *1 point*
t(4;14): *1 point*
1q+: *0.5 points*

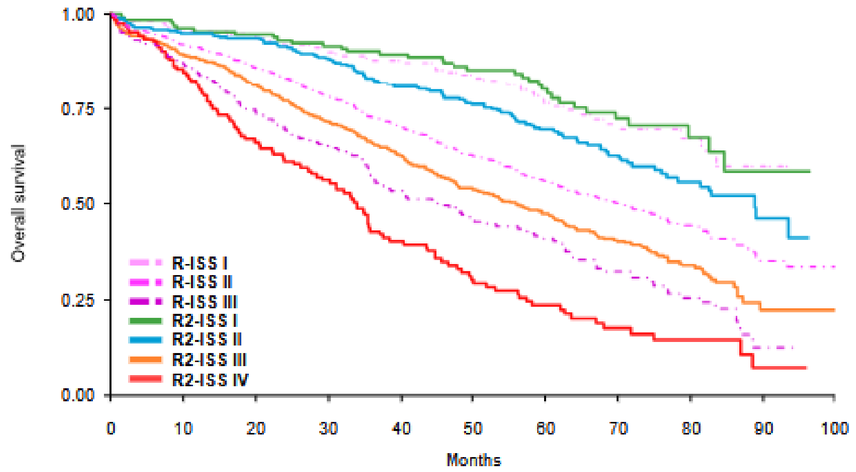
Groups:
Low risk: 0
Low-intermediate: 0.5-1
Intermediate-high: 1.5-2.5
High: 3-5

1975 — 2017 — 2021 — 2025

Greipp PR et al. JCO 2005, Palumbo A et al. JCO 2015, D'Agostino M et al. JCO 2022

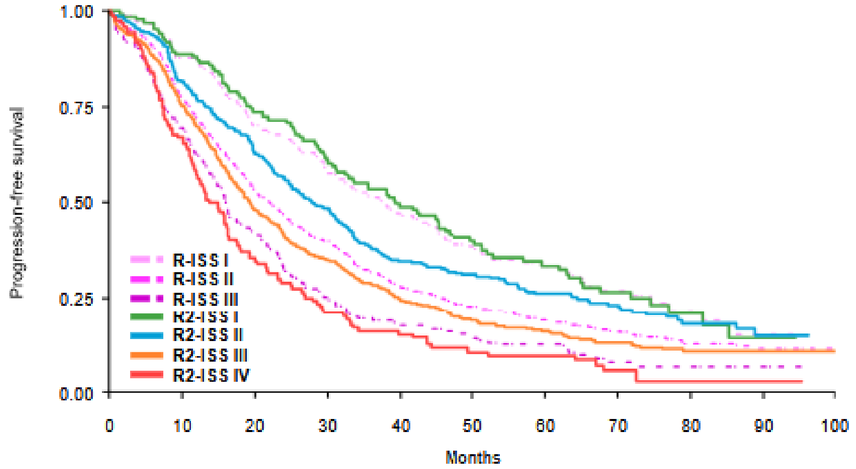
R2-ISS improved better risk stratification

S6c. OS - Validation set



	% pts	mOS	mPFS
R2-ISS I	19.2%	NR	68 months
R2-ISS II	30.8%	109 months	45 months
R2-ISS III	41.2%	68 months	30 months
R2-ISS IV	8.8%	38 months	20 months

S6d. PFS - Validation set



R-ISS distribution according to the R2-ISS in evaluable patients included in the training set (n=2226)

Prognostic score	R2-ISS low (I, n=428)	R2-ISS low-int (II, n=686)	R2-ISS int-high (III, n=917)	R2-ISS high (IV, n=195)
R-ISS I	428	169	0	0
R-ISS II	0	517	811	44
R-ISS III	0	0	106	151

D'Agostino M et al. JCO 2022, data supplement

Risk stratification – coming soon

1

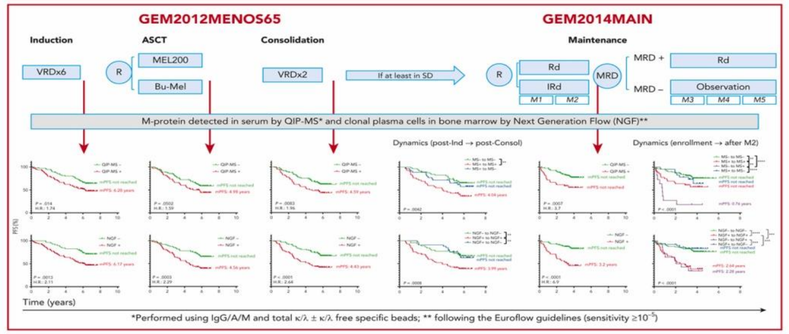
Box 1 | Summary of the IMS–IMWG 2024 consensus definition of high-risk MM

- del(17p)[a] and/or *TP53* mutation[b]
- t(4;14), t(14;16) or t(14;20), co-occurring with +1q[c] and/or del(1p32)
- Monoallelic del(1p32) along with 1q gain, or biallelic del(1p32)
- High β_2 microglobulin (>5.5 mg/dl) with normal creatinine (<1.2 mg/dl)

IMS, International Myeloma Society; IMWG, International Myeloma Working Group; MM, multiple myeloma. [a]Cancer clonal fraction ≥20%, by analyses conducted on CD138-positive/purified cells. [b]Assessed using a next-generation sequencing-based method. [c]+1q refers to gain (three copies) or amplification (four or more copies) of the long arm of chromosome 1. See ref. 15.

2

Measurable Residual Disease by Mass spectrometry and Next Generation Flow Cytometry to Assess Treatment Response in Patients with Multiple Myeloma

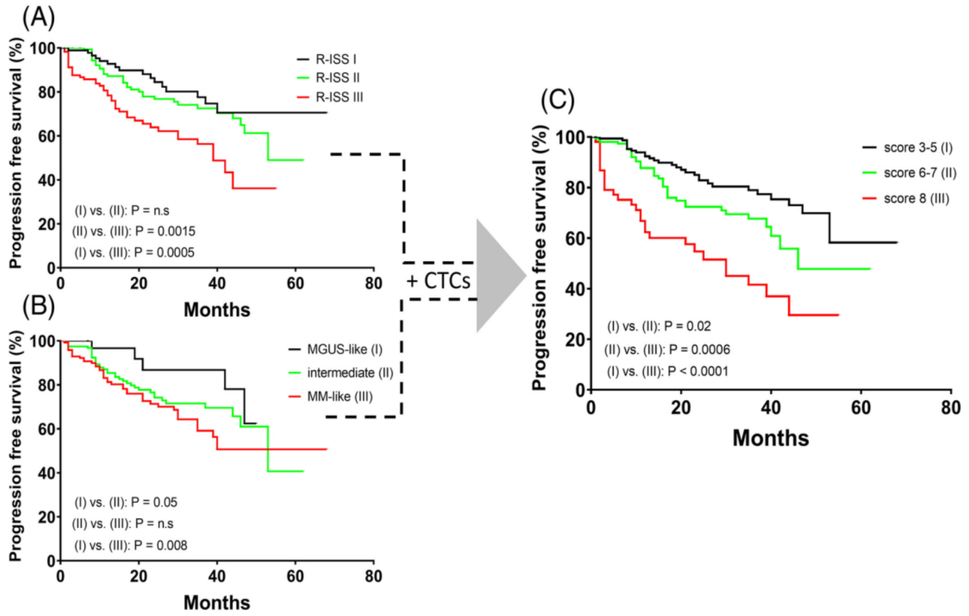


Conclusion: MRD evaluation by either NGF or MS achieves similar prognostic value based on single-time-point assessments and kinetics.

*Puig et al. DOI: 10.1182/**blood**.2024024995*

blood Visual Abstract

3

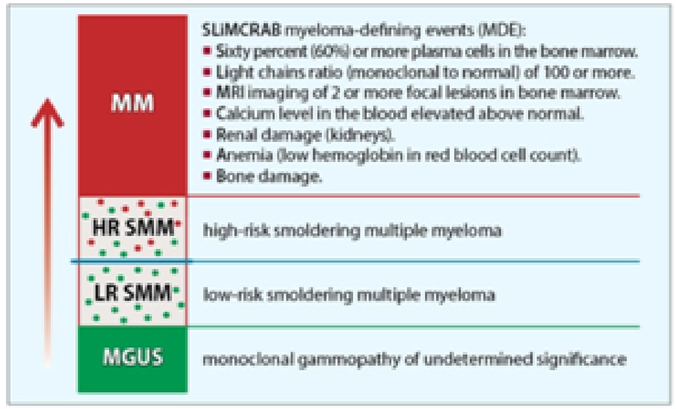


The combination of CPCs assessment with ISS might further improve disease staging

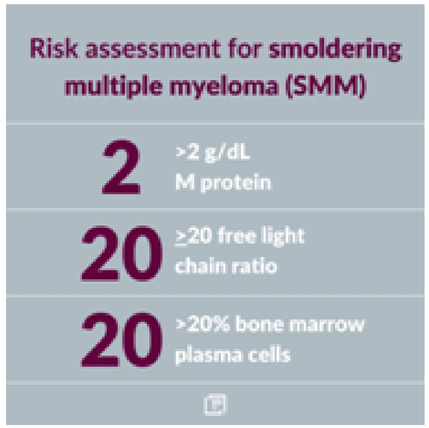
MRD evaluation by NGF and MS achieves similar prognostic value based in single time point assessments and kinetics. Thus, the minimally invasive nature of MRD monitoring by MS represents a breakthrough in highly sensitive response assessment in MM

Avet-Loiseau H et al. JCO, 2025, Kostopoulos IV et al. Am J Hematol, 2024, Puig et al. Blood 2024

Risk stratification – SMM



Three-factor model



Mayo Clinc criteria, 2018

Four-factor model

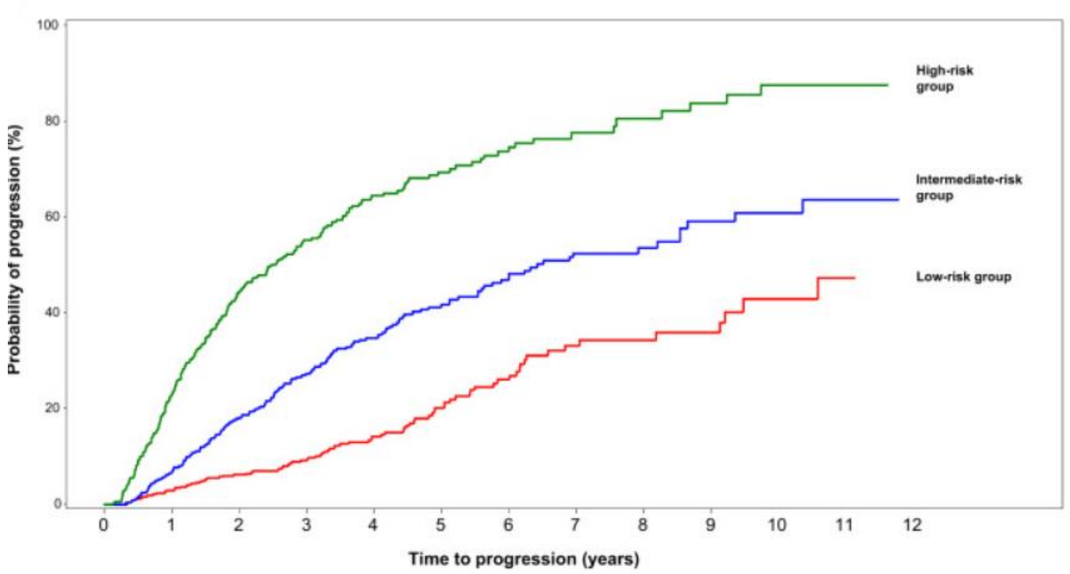
2/20/20 criteria + cytogenetic abnormalities:

- (t(4;14)
- t(14;16)
- +1q and/or del13q

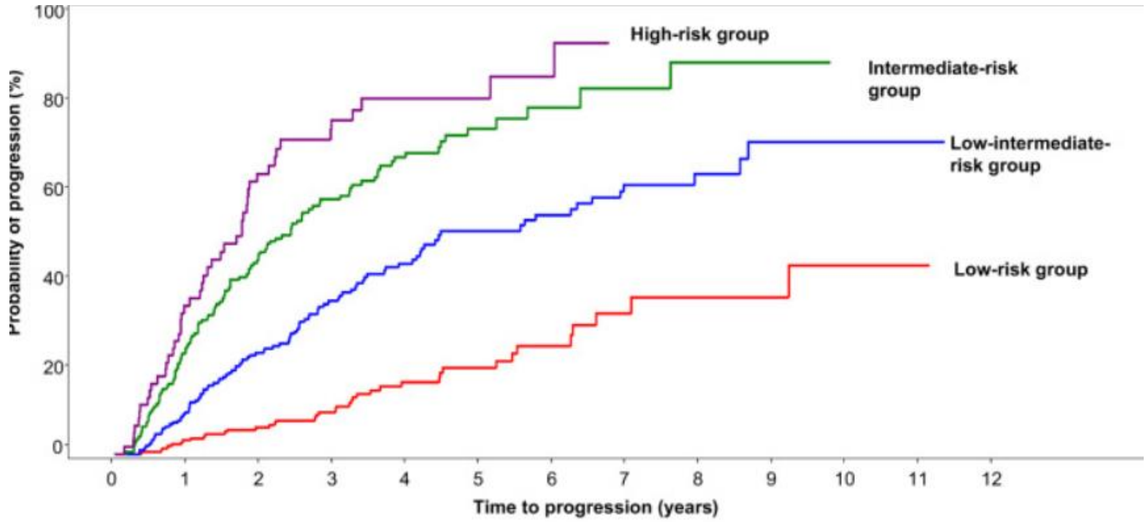
IMWG risk stratification for SMM, 2020

Mateos MV IV et al. Blood Cancer J, 2020

Risk stratification – SMM



Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low-Risk	0	Reference	6.2%	522 (38.3%)
Intermediate	1	2.99 (1.97 – 4.54)	17.9%	445 (32.7%)
High	2-3	9.02 (6.15 – 13.2)	44.2%	396 (29.1%)



Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low	0	Reference	6.0%	225 (32.7%)
Low-intermediate	1	4.16 (2.26 – 7.67)	22.8%	224 (32.5%)
Intermediate	2	9.82 (5.46 – 17.7)	45.5%	177 (25.7%)
High	3-4	15.5 (8.23 – 29.0)	63.1%	63 (9.1%)

Mateos MV IV et al. Blood Cancer J, 2020

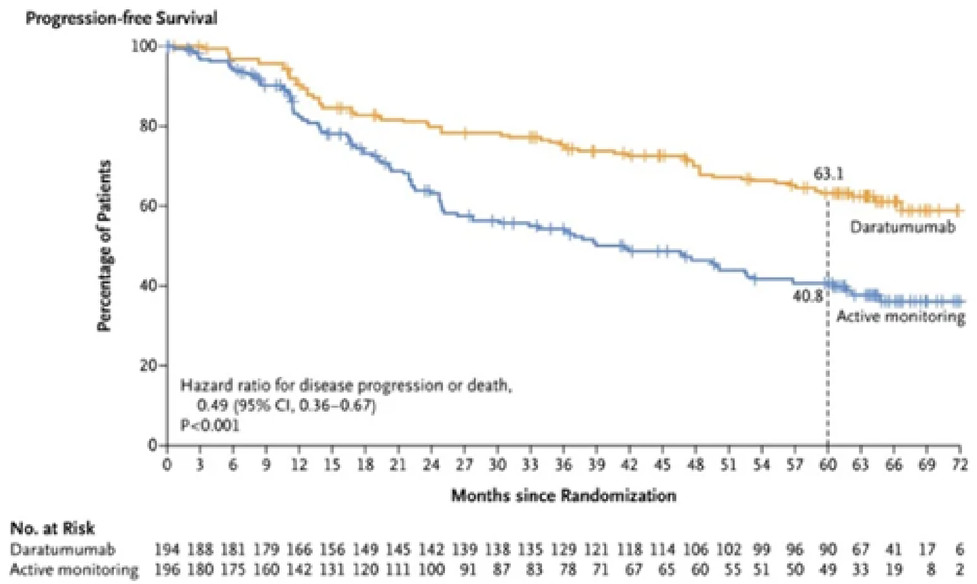
Smouldering MM – Time for Treatment?

2010-2020

Two Indipendent phase III trials in HR SMM treated with Rd or R (3-factors model) showed better PFS

2024

Phase III AQUILA trial showed better PFS in SMM high risk* treated with daratumumab sc



2027?

Curative intent treatment:

Phase II CESAR trial, 2024

Phase II ASCENT trial

Phase II LINKER SMM1

Phase II CAR PRISM

FDA 2025

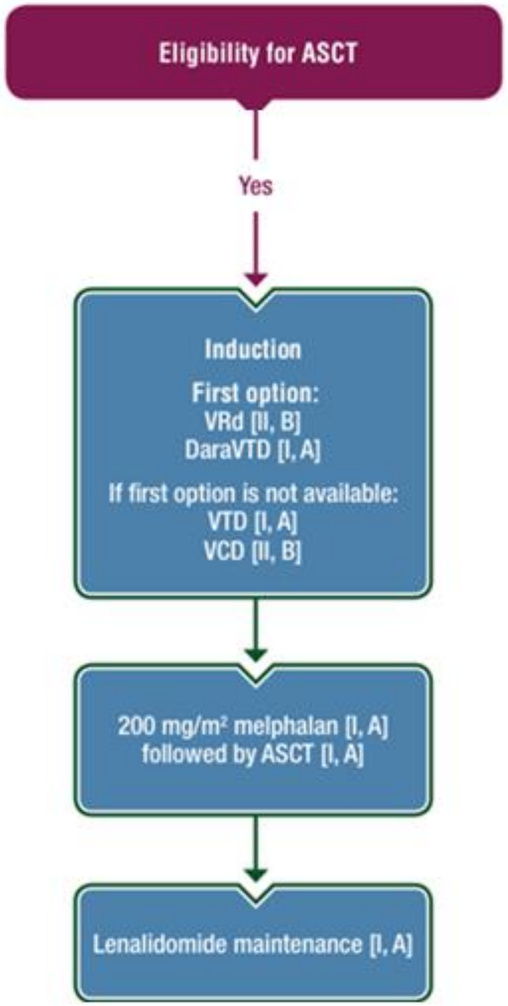
Mateos MV et al. NEJM, 2010, Lonial S et al. JCO, 2020, Dimopoulos MA et al. NEJM, 2024

Smouldering MM – Curative approach

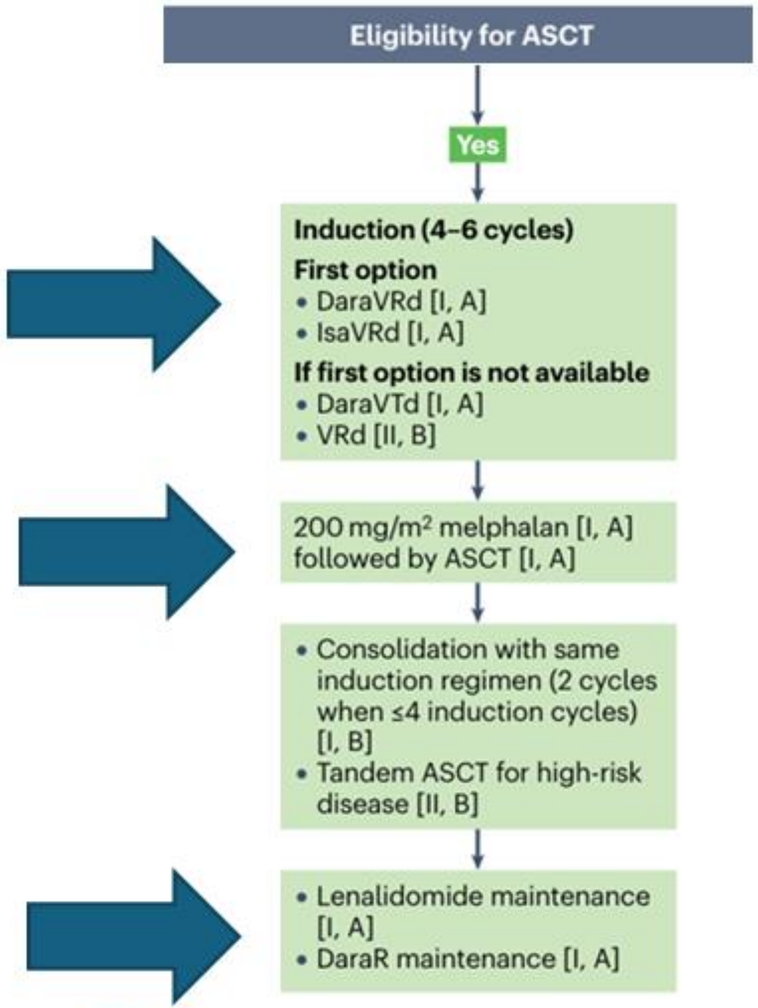
STUDY	N°pts	HR SMMM criteria	Therapy	% MRD
CESAR	90	Mayo 2018	KRd-ASCT-KRD-R for 2 ys	62
ASCENT	87	Mayo 2018	DKRd-ASCT-DKRd-DRd x 1y	84
LINKER SMM1 (m-fup 12.7 months)	24	Mayo 2018 + PETHEMA	Linvoseltamab x 2 ys	100 after 1 cycle (106)
CAR PRISM (m-fup 15.3 months)	20	Mayo 2018 + IMWG	Ciltacel	100 (106)

Mateos eta l. J Clin Oncol 2024, Kumar et al Blood2022, Rodriguez Otero et al Blood 2023, Nademm et al Nature 2026

Intensity of first-line therapy : 1st line for TE patients



2021 *Dimopoulos MA et al. Ann Oncol, 2022*



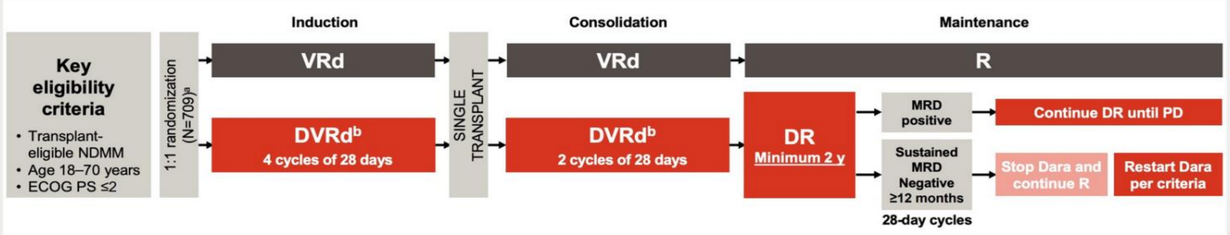
2025 *Dimopoulos MA et al. . Nat Rev Clin Oncol, 2025*

Intensity of first-line therapy : 1st line for TE patients

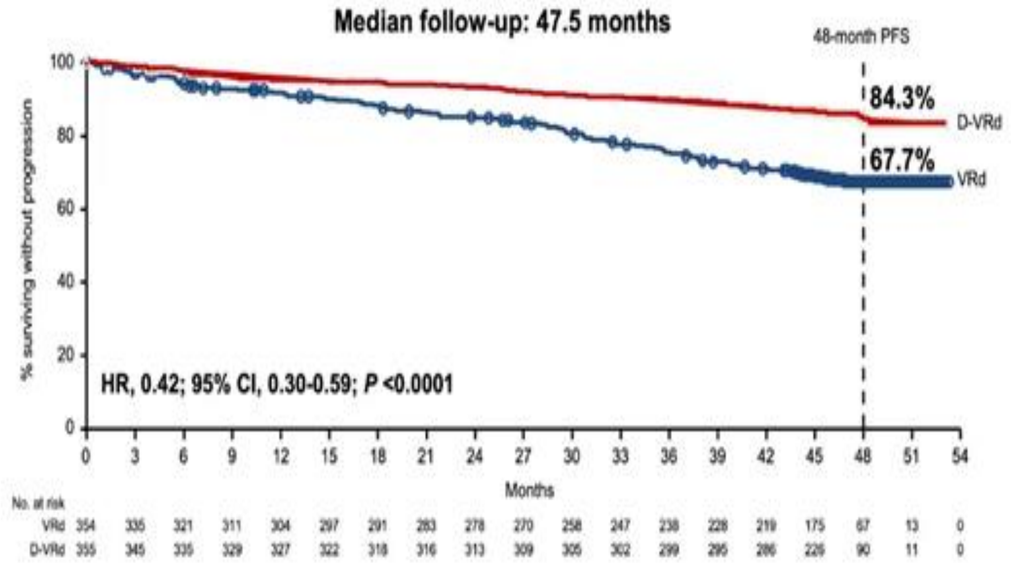
- To date, DaraVRd and IsaVRD, among quadruplets, are recommended as the new SOC regimens. For all induction regimen, 4 to 6 cycles are recommended
- Collection of HSCs should be performed after three or four induction cycles
- Tandem ASCT might be suitable in genetically defined high –risk disease or in all patients who received induction with VCd
- On the basis of PFS results from PERSEUS trial, Dara-R is the new SOC maintenance
- Very limited role of AlloSCT

Intensity of first-line therapy : 1st line for TE patients

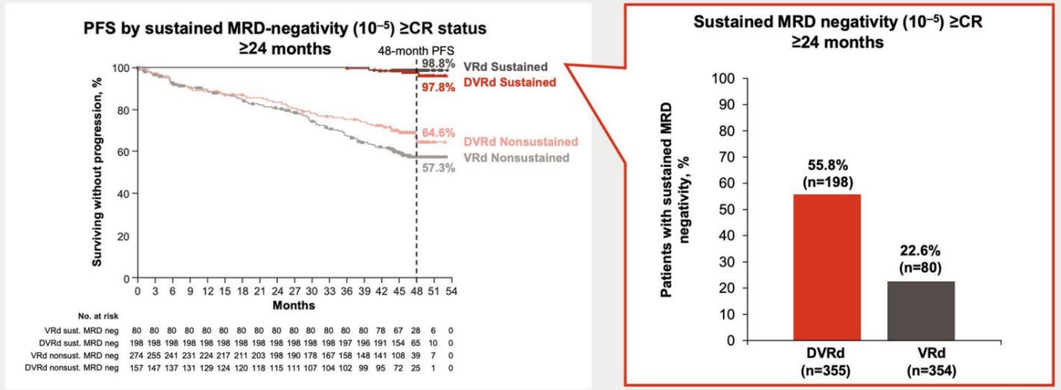
PERSEUS: Study Design



- MRD-negativity[c] rate was defined as the proportion of patients achieving MRD negativity and ≥CR in the ITT population
  - Patients who were not evaluable or had indeterminate results were considered MRD positive
  - MRD was evaluated post consolidation[d] at the time of suspected CR/sCR; at 12, 18, 24, 30, and 36 months after cycle 1 day 1; and yearly thereafter[e]



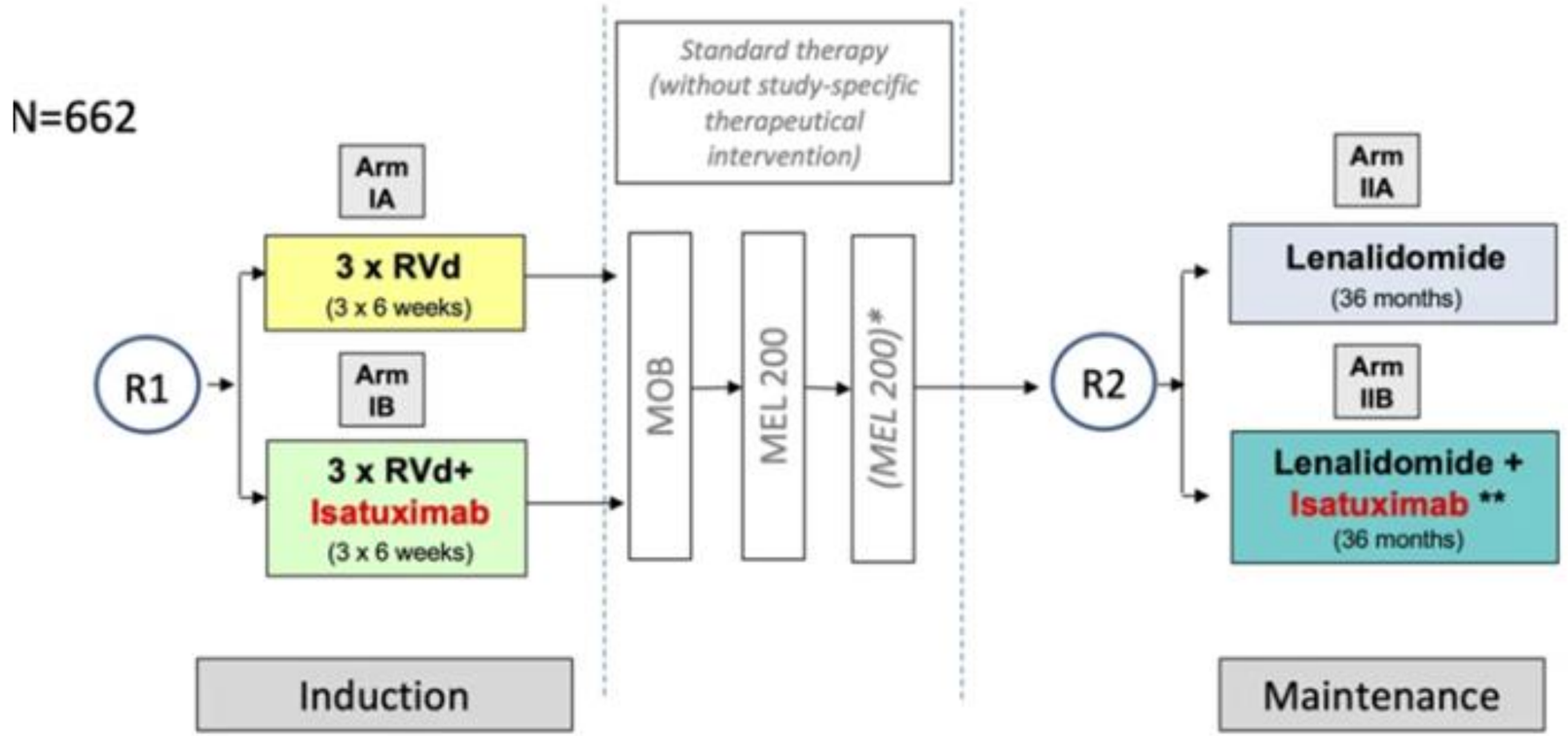
PFS by Sustained MRD-Negativity (10^{-5}) ≥CR Status at ≥24 months



- Sustained MRD-negativity (10^{-5}) ≥CR rates for ≥24 months were more than twice as high with DVRd vs VRd
- Among these patients, 48-month PFS rates exceeded 95% in both arms

Presented by P. Moreau et ASCO 2025

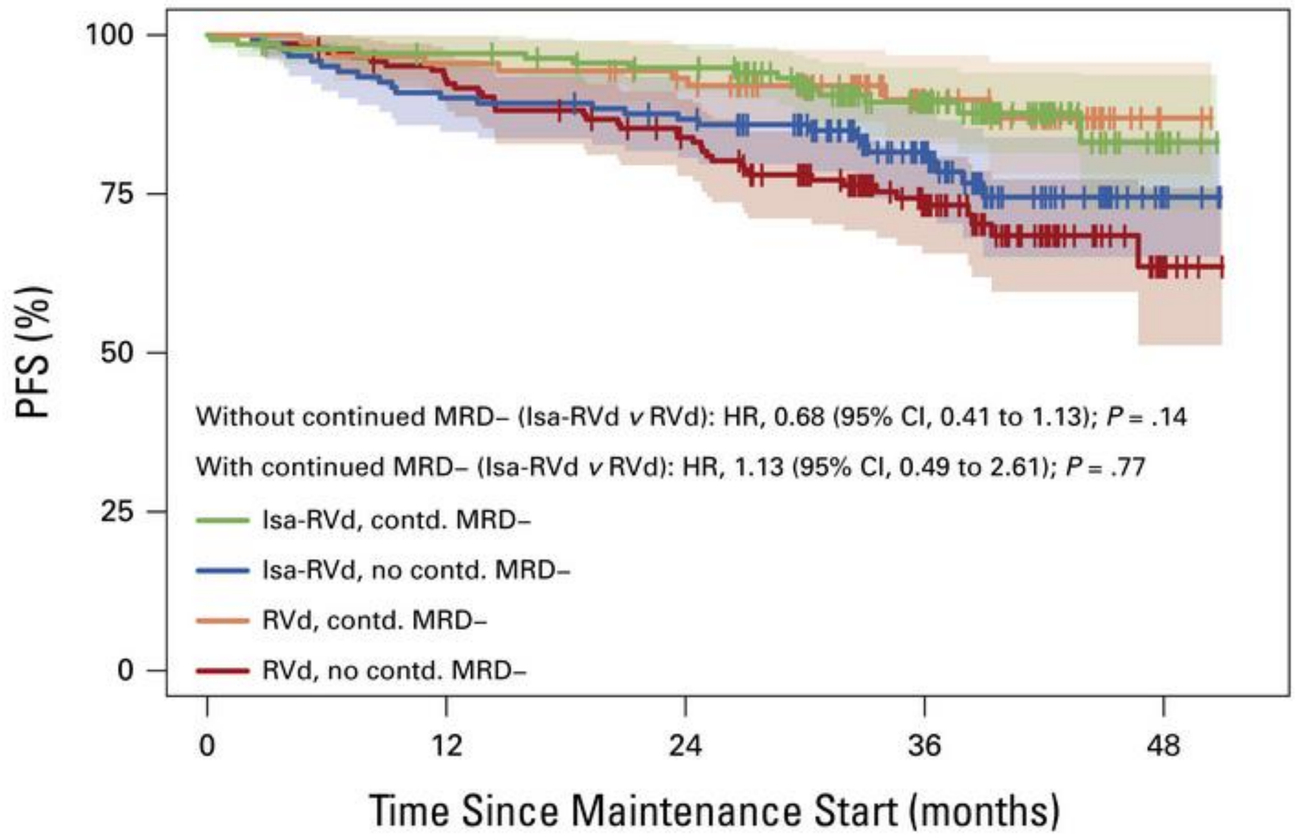
Intensity of first-line therapy : The disruptive role of anti CD38 in maintenance



Goldschmidt et al. ASH 2024

Intensity of first-line therapy : The disruptive role of anti CD38 in maintenance

GMMG-HD7 trial



Number at risk (censored):					
Isa-RVd, contd. MRD–	138 (0)	132 (2)	125 (4)	64 (55)	5 (57)
Isa-RVd, no contd. MRD–	122 (0)	109 (1)	103 (2)	59 (39)	5 (50)
RVd, contd. MRD–	89 (0)	85 (0)	79 (4)	35 (42)	2 (32)
RVd, no contd. MRD–	145 (0)	133 (2)	115 (5)	64 (38)	6 (54)

Mai et al. J Clin Oncol **43**, 1279-1288(2025)

Intensity of first-line therapy : The disruptive role of anti CD38 in maintenance

AURIGA trial

Key Inclusion Criteria

- Age 18-79 years
- NDMM with ≥4 cycles of induction therapy
- ≥VGPR at screening[a]
- MRD positive (10^{-5}) post-ASCT[b] at the time of screening
- Randomization within 6 months of ASCT date
- HDT and ASCT within 12 months of the start of the induction treatment
- ECOG PS ≤2

Key Exclusion Criteria

- Prior anti-CD38 antibody exposure

1:1 Randomization (N = 200)

28-day cycles

Maintenance: up to 36 cycles[c] (28-day cycles)

D-R
D: 1800 mg SC[d] QW in cycles 1-2, Q2W in cycles 3-6, Q4W in cycles 7+
+
R: 10 mg PO QD[e] on days 1-28

R
10 mg PO QD[e] on days 1-28

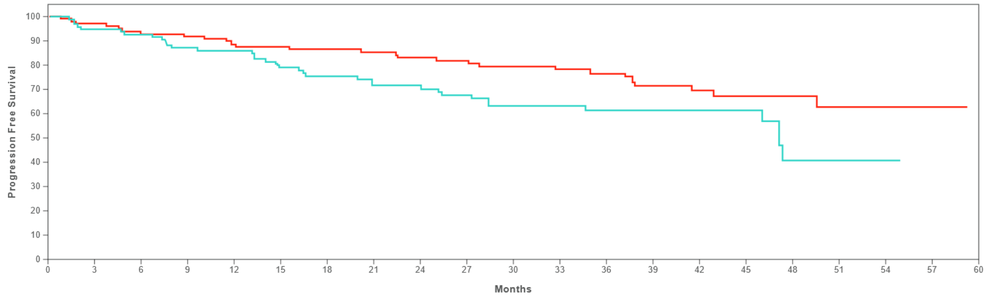
Continue until unacceptable toxicity, disease progression, consent withdrawal, or for a maximum of 36 cycles

Primary Endpoint

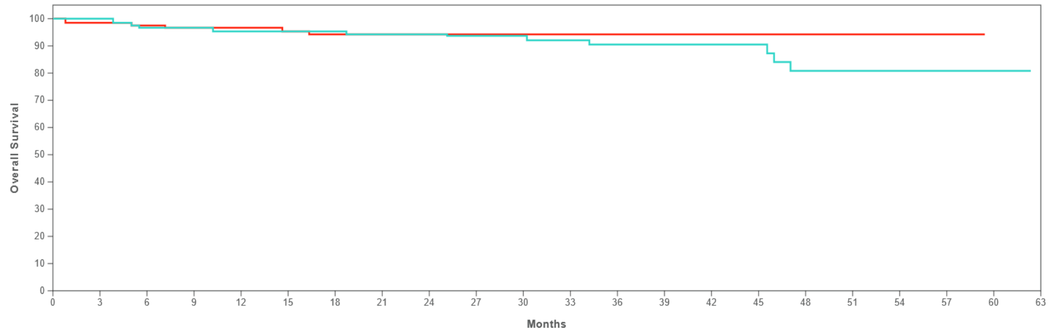
- MRD-negativity (10^{-5}) conversion rate from baseline to 12 months[e]
  - MRD assessed at 12, 18, 24, and 36 months

Key Secondary Endpoints

- Safety
- PFS
- Overall MRD-negativity conversion rate
- Sustained MRD-negativity rate (≥6 months)
- Response rates including CR/sCR[a]
- Duration of ≥CR
- OS
- HRQoL changes based on PROs



Interval	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Lenalidomide + Da… Dar: Q2W, C1 and …	99	93	90	88	85	83	82	80	73	70	61	60	49	39	31	27	18	12	7	3	0
Lenalidomide D1 to D28, each 28…	101	88	85	78	75	66	63	58	53	49	41	40	30	28	20	16	6	5	2	0	0

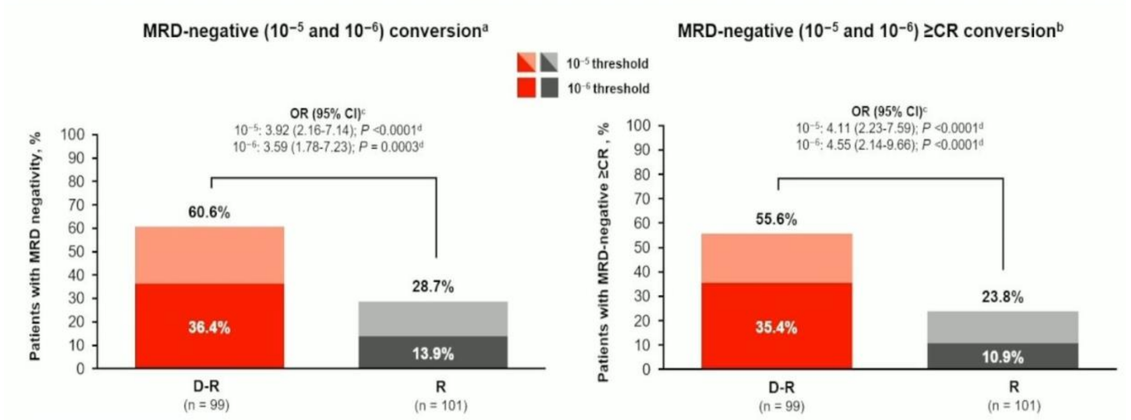


Interval	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
Lenalidomide + Da… Dar: Q2W, C1 and …	99	94	93	92	92	90	88	87	85	82	77	74	61	56	46	37	25	18	12	4	0	0
Lenalidomide D1 to D28, each 28…	101	95	91	89	88	88	87	84	79	75	67	64	54	47	37	31	20	14	7	3	1	0

Andersen Jr et al. 2025

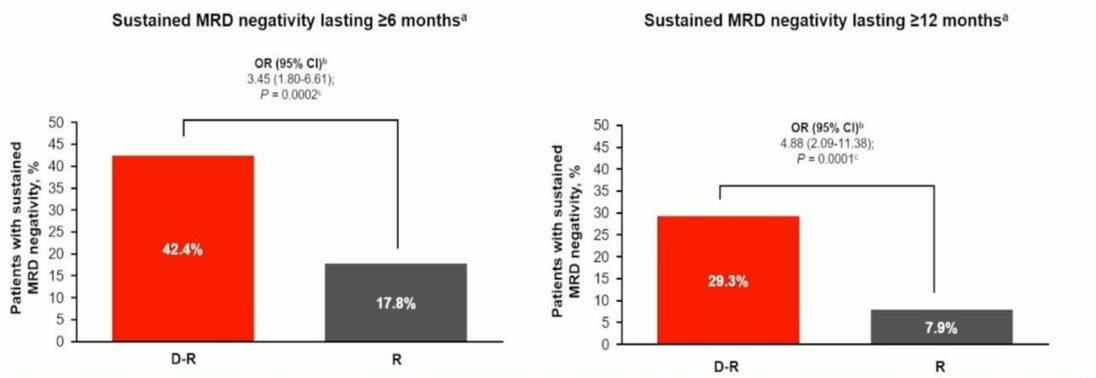
Intensity of first-line therapy : The disruptive role of anti CD38 in maintenance

AURIGA: MRD-Negative (10^{-5} and 10^{-6}) Conversion Rates



After ≥24 months of D-R maintenance, MRD-negative conversion rates continued to be more than double at both the 10^{-5} and 10^{-6} thresholds compared with R alone

AURIGA: Sustained MRD-Negative (10^{-5}) Rates



More than double and almost quadruple the ≥6-month and ≥12-month sustained MRD-negativity rates at 10^{-5}, respectively, were seen with D-R maintenance versus R alone

Andersen Jr et al. 2025

Intensity of first-line therapy: from “what’s new to what’s next”

The substitution of bortezomib with carfilzomib in quadruplet regimens has resulted in excellent MRD negativity rates, especially in patients with high-risk disease

- Data from not registrative trials-

GMMG concept: phase II trial of IsaKrd for NDMM

MRD-neg rate after consolidation of **73.2**% in the MRD-analysis population (153/209; 10 not assessable). Further analyses confirmed the benefit across different CA subgroups. With a median follow-up (mFU) of 42 mo (0-85.5 mo**), mPFS for TE pts was 69.7 mo**, while mOS has not been reached. **For TNE pts (mFU 60 mo), mPFS and mOS have not been reached**.

ISKIA phase III trial of IsaKRd for TE NDMM

MIDAS

Leypoldt et al. EHA Library 06/15/2025; 4159286; S209

Intensity of first-line therapy: from “what’s new to what’s next”

The substitution of bortezomib with carfilzomib in quadruplet regimens has resulted in excellent MRD negativity rates, especially in patients with high-risk disease

- Data from not registrative trials-

GMMG concept: phase II trial of IsaKrd for NDMM

ISKIA phase III trial of IsaKRd for TE NDMM

MIDAS

	Post induction		Post ASCT		Post-ASCT full-dose consolidation		Post light consolidation		1-year sustained MRD negativity	
	Isa-KRd (*n* = 151)	KRd (*n* = 151)	Isa-KRd (*n* = 151)	KRd (*n* = 151)	Isa-KRd (*n* = 151)	KRd (*n* = 151)	Isa-KRd (*n* = 151)	KRd (*n* = 151)	Isa-KRd (*n* = 151)	KRd (*n* = 151)
10^{-5} MRD (95% CI)	46% (38%–54%)	27% (20%–35%)	64% (56%–72%)	50% (41%–58%)	77% (69%–83%)	67% (59%–74%)	79% (71%–85%)	74% (66%–81%)	66% (57%–73%)	59% (51%–67%)
10^{-6} MRD (95% CI)	28% (21%–36%)	14% (9%–20%)	52% (44%–60%)	27% (20%–35%)	68% (59%–75%)	48% (40%–56%)	74% (66%–80%)	64% (55%–71%)	52% (44%–60%)	38% (31%–47%)

Gay et al. Nature 2026

Intensity of first-line therapy: from “what’s new to what’s next”

The substitution of bortezomib with carfilzomib in quadruplet regimens has resulted in excellent MRD negativity rates, especially in patients with high-risk disease

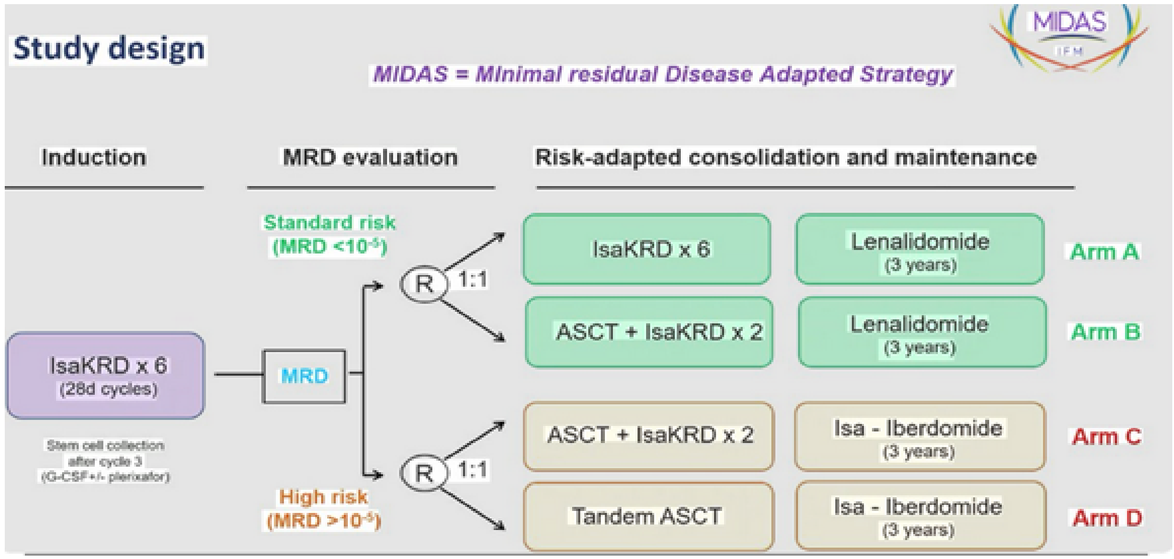
- Data from not registrative trials-

GMMG concept: phase II trial of IsaKrd for NDMM

ISKIA phase III trial of IsaKRd for TE NDMM

MIDAS phase III trial of IsaKRd for TE NDMM

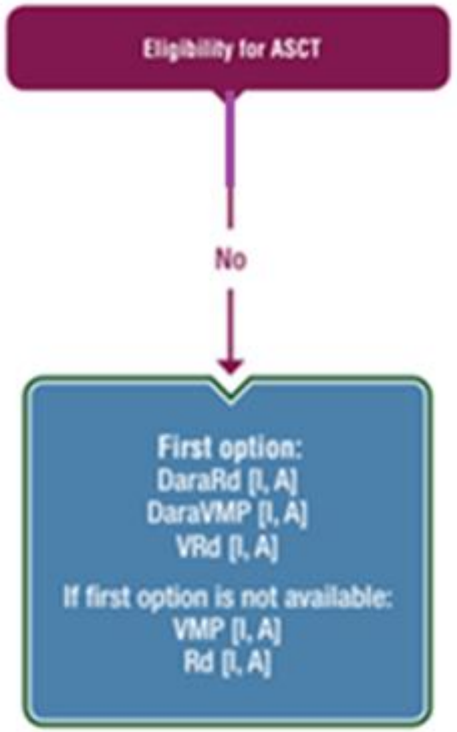
Mrd negativity rate after induction:
63% (10-5, 47% 10-6)



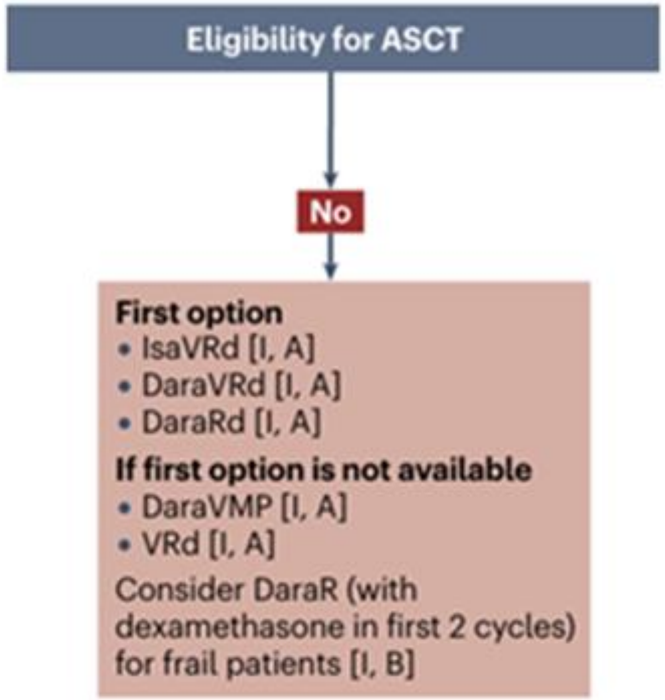
Mrd negativity 10-6 prior to maintenance
84%
86%
40%
32%

Perrot et al. Blood 2025

Intensity of first-line therapy : 1st line for NTE patients



2021 *Dimopoulos MA et al. Ann Oncol, 2022*



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

Intensity of first-line therapy : 1st line for NTE patients

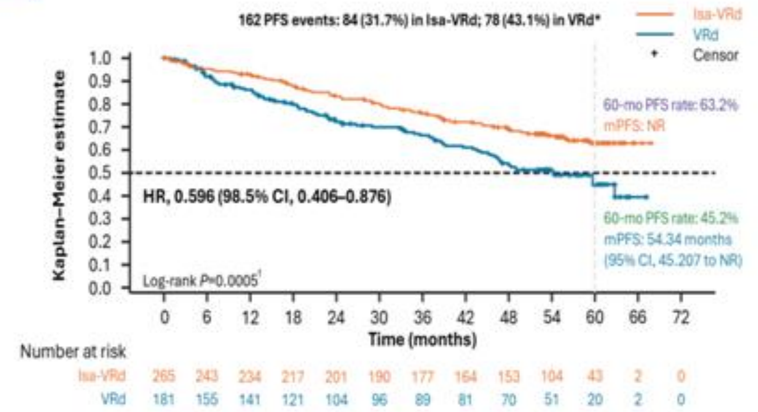
Patients < 80 years old and with IMWG FS < 2 can receive the new SOC regimens: IsaVRd and DaraVRd

DRd is an option in all NTE with IMWG FS ≥ 1

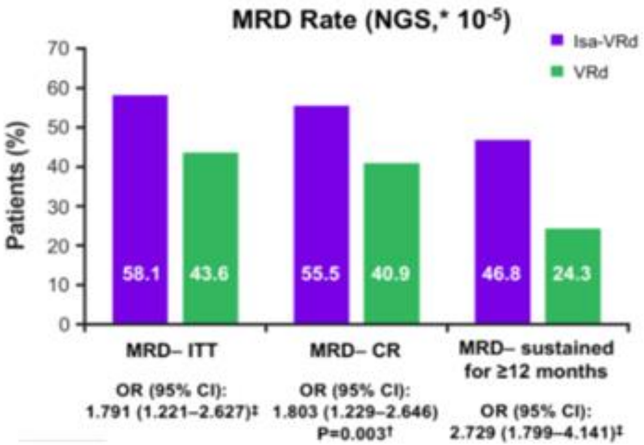
Dose adaption schedule/dose intensity modulation for bortezomib and dexamethasone sparing strategy

Intensity of first-line therapy : 1st line for NTE patients

IMROZ

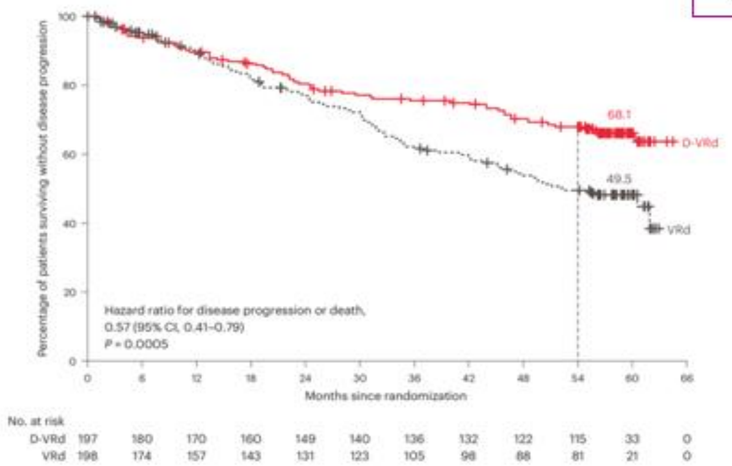


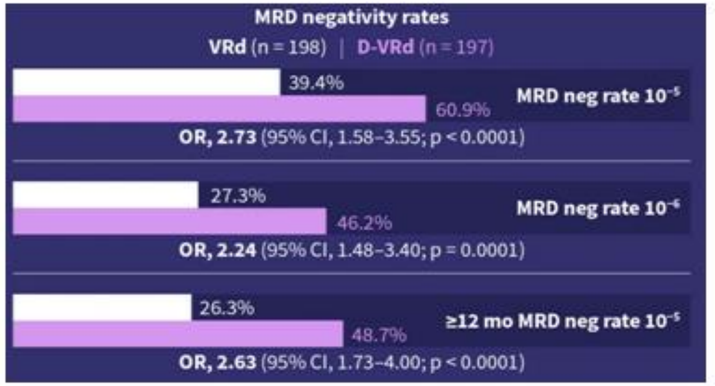
At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%



Facon et al. N Eng J Med 2024

CEPHEUS





Usmani et al. Nature 2025

Intensity of first-line therapy : 1st line for NTE patients

ARE QUADRUPLETS FIT FOR FRAIL PATIENTS?

Dose adaption schedule/dose intensity modulation for bortezomib and dexamethasone sparing strategy

	MAIA trial	REST trial
% MRD neg in > 80ys pts	23,8%	31%

Facon et al. Leukemia 2022, Askeland et al. Lancet Haematol 2025

Early use in immunotherapies in relapses

"Patients who have not received lenalidomide or have disease sensitive o this drug should receive regimens that have been recommended in the 2021 EHA guidelines"

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.

Randomized studies with Rd control arm

Early use in immunotherapies in relapses

RRMM – evolving scenario: antiCD38 exposition/refractoriness and its impact

Mina et al., Clin Lymph, Myeloma and Leukemia 2025

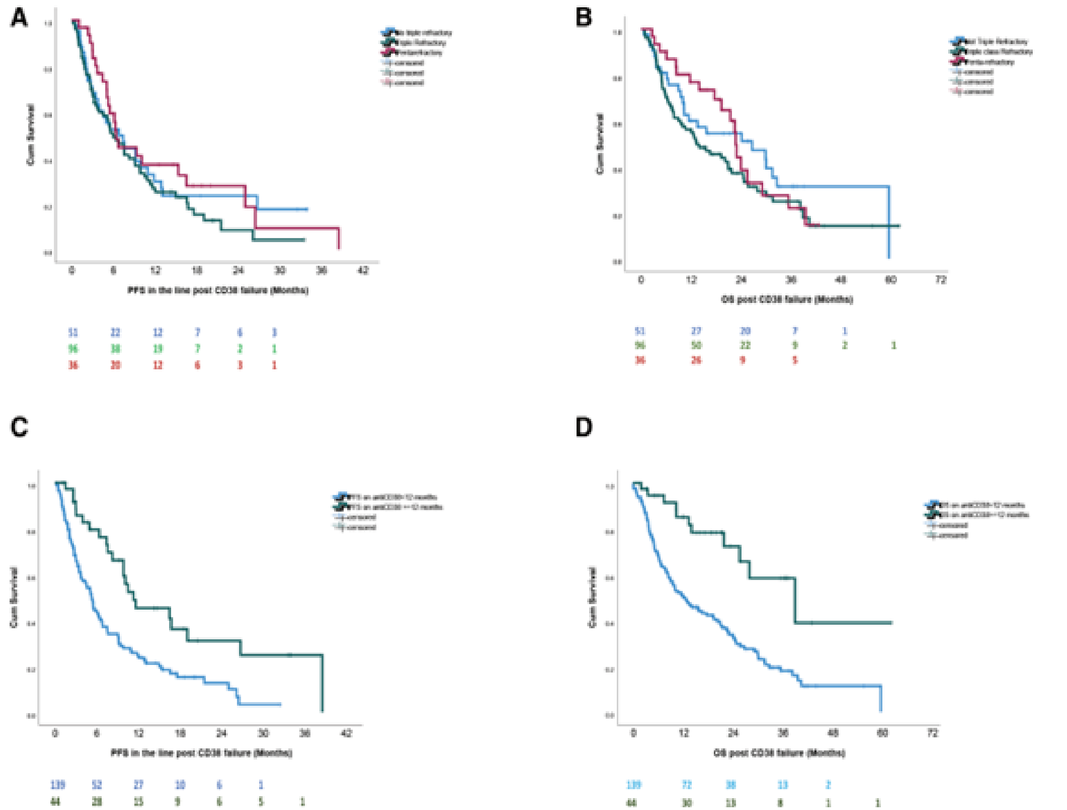
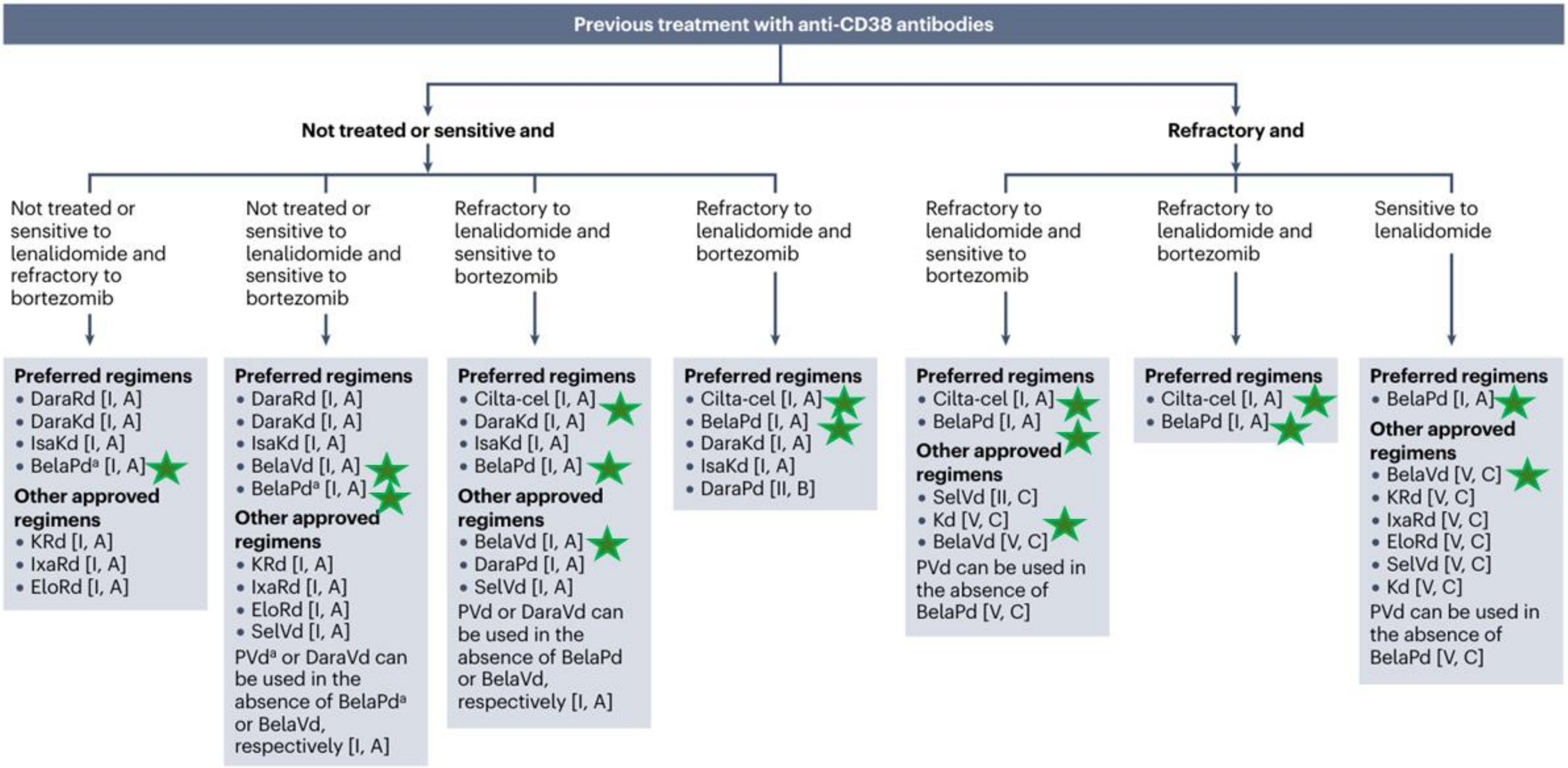


Figure 1. Outcomes of patients after failure of anti-CD38 therapy. (A) PFS in the line of therapy post-anti-CD38 failure and (B) OS after anti-CD38 failure, for non-triple-class refractory, triple-class refractory, and penta-refractory patients (C) PFS in the line of therapy post-anti-CD38 failure and (D) OS after anti-CD38 failure for patients who had duration of PFS in the index anti-CD38-based therapy that lasted more or less than 12 months. OS = overall survival; PFS = progression free survival.

Kastritis et al. Hemasphere 2025

Early use in immunotherapies in relapses



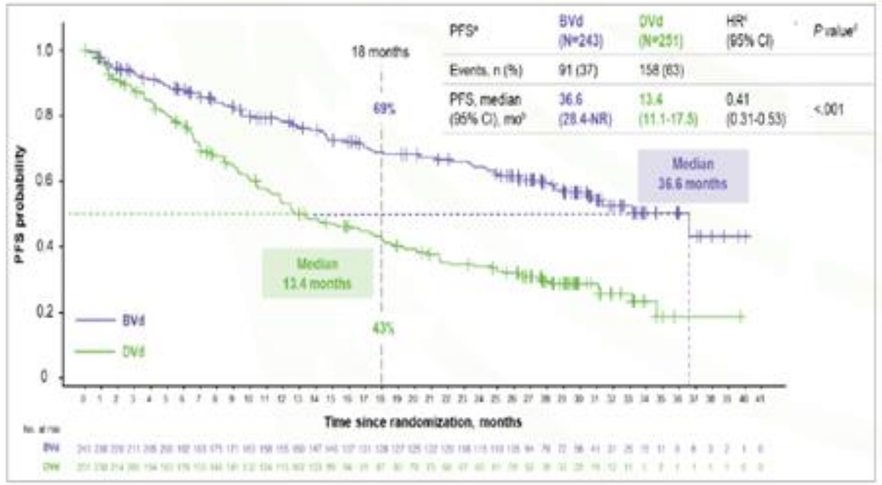
Dimopoulos MA et al. Nat Rev Clin Oncol, 2025

Early use in immunotherapies in relapses

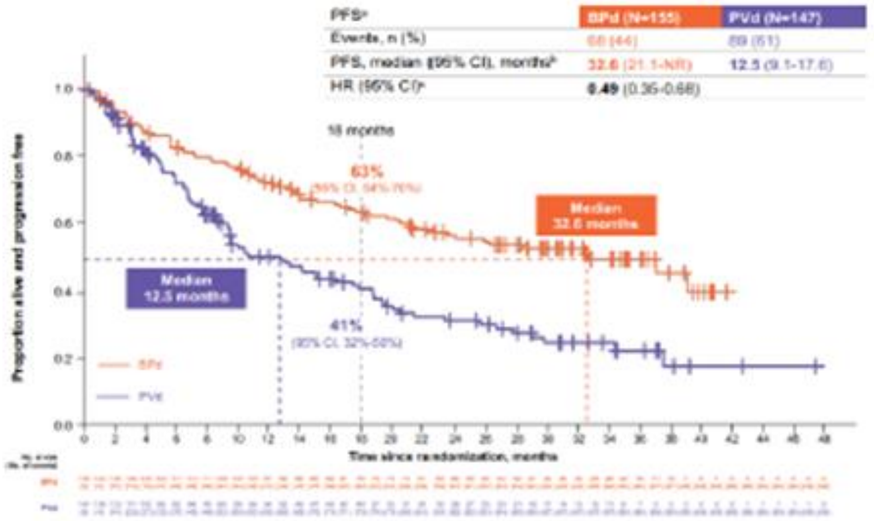
" Classical " treatment strategies in Lena refractory MM patients

Regimen	Trial	mPFS (months)	% R refractory patients	mPFS in R refractory patients
Kd	Endeavor	18.7	25	8.6
DVd	Castor	16.7	24	7.8
DKd	Candor	28.4	32	28.1
Isakd	Ikema	35.7	32	HR 0.6
SVd	Boston	13.2	37	10.2
DPd	Apollo/Maia	12.4/23.7	63-76%	9.9/23
PVd	Optimism	11.7	71%	17.8

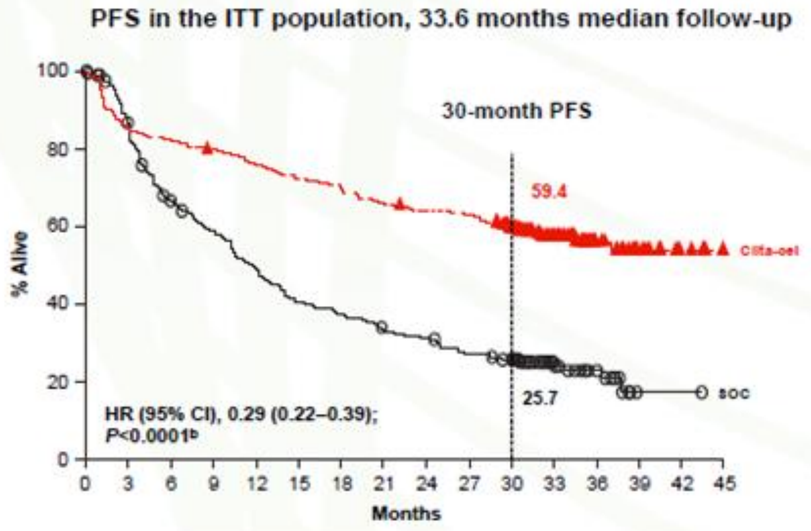
Early use in immunotherapies in relapses



DreaMM-7



DreaMM-8



Cartitude-4

Hungria V et al. NEJM 2024, Dimopoulos MA et al. NEJM 2024; Popat et al. Ash 2024

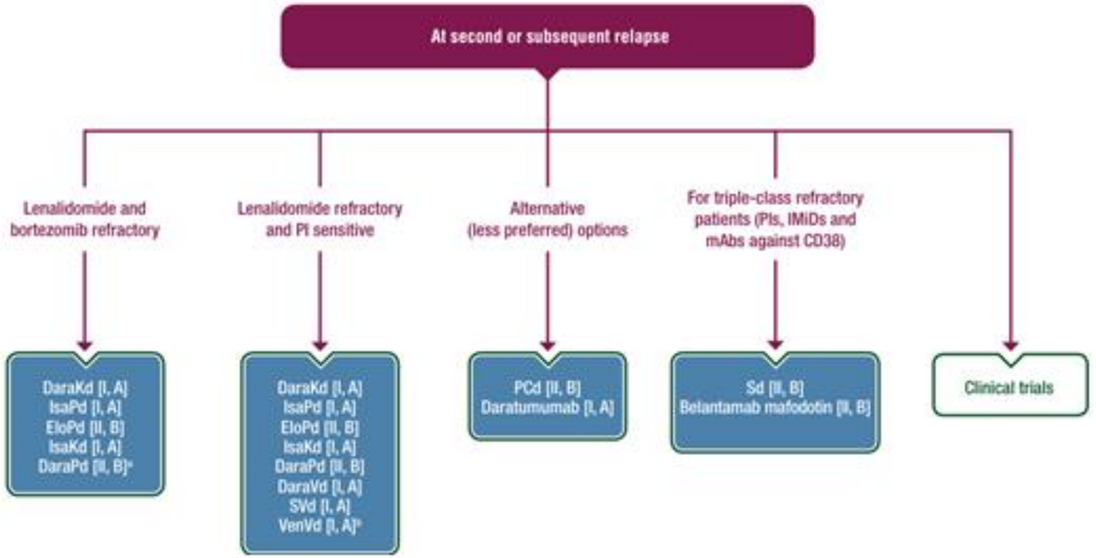
Early use in immunotherapies in relapses

New immunotherapies for MM patients in first relapse

Regimen	Trial	mPFS (months)	% R ref patients	mPFS in R refractory	% Dara Ref patients	mPFS TCR
Ciltacel	Cartitude-4	NR	100	NR	23 (14% TCR)	19
BelaPd	DreaMM-8/ Algonquin*	32.6	81	32	23 (exposed)	19,6 *
BelaVd	DreaMM-7	35.7	33	25	few	/

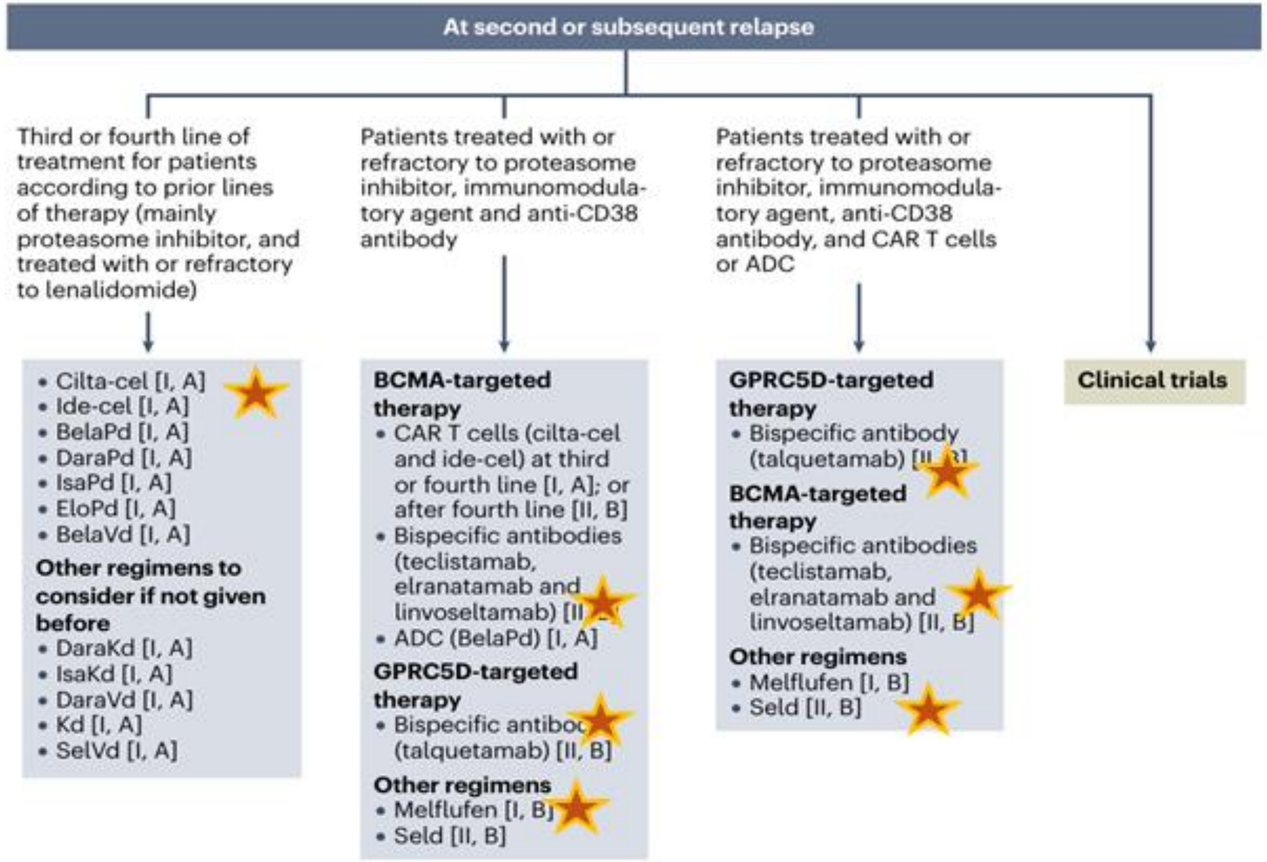
Hungria V et al. NEJM 2024, Dimopoulos MA et al. NEJM 2024; Trudel et al. Nat Med 2024 Popat et al. Ash 2024

Use of immunotherapies in 2nd or more advanced relapses



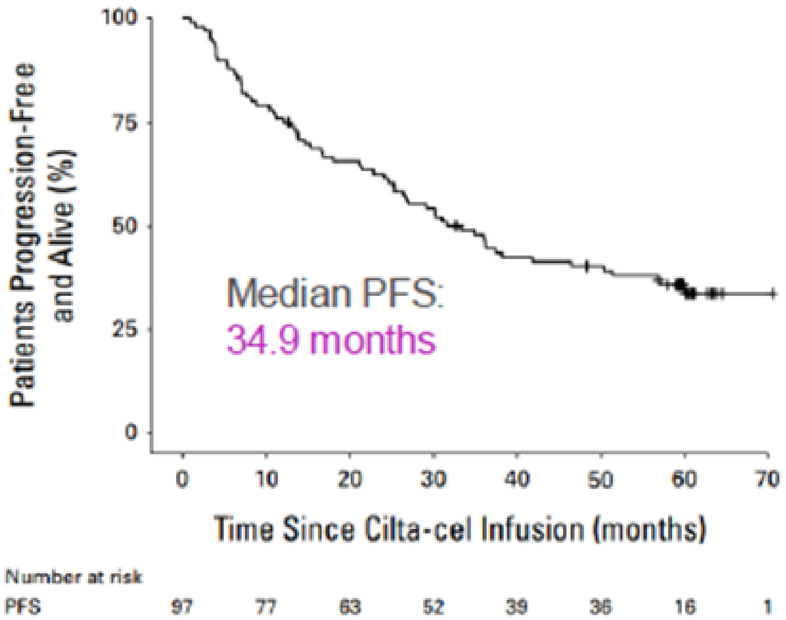
In the third or fourth line of treatment, patients can receive treatments that they have not been previously exposed to, including cilta-cel, ide-cel, BelaPd, DaraPd, IsaPd, EloPd, BelaVd [I, A] or other regimens (Fig. 3).

Retreatment with an anti-CD38 antibody after disease progression on this therapeutic class is not recommended. If such a retreatment strategy is the only option, it should be started only after an anti-CD38 antibody-free interval of ≥1 year [panel consensus; IV, C].



Dimopoulos MA et al. Ann Oncol, 2022, *Dimopoulos MA et al. Nat Rev Clin Oncol, 2025*

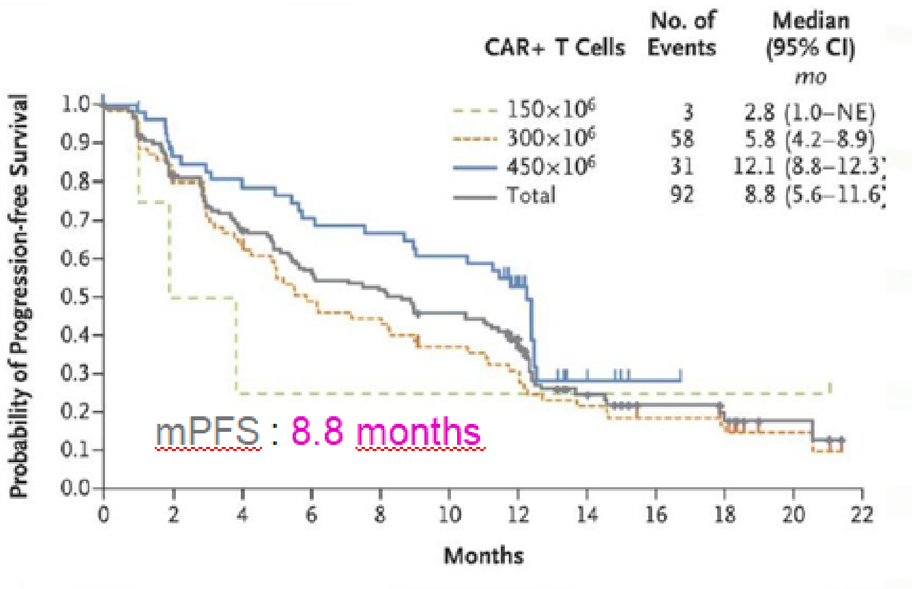
Use of immunotherapies in 2nd or more advanced relapses



CARTITUDE -1 Ib/II trial: efficacy and safety of cilta-cel in TCE RRMM, ≥3 prior LOT *or double refractory to PI + IMiD* , median of 6 prior lines of therapy , 88% TCR.

Led to EMA approval of cilta-cel in patients with **≥3 prior therapies**, including IMiD, PI, and anti-CD38 mAb and had disease progression on the last therapy.

HR cytogenetics and EMD were equally likely to be progression-free at 5 yrs. These data **provide the first evidence that cilta-cel is potentially curative in patients with RRMM**



KarMMa phase II study: efficacy and safety of ide-cel at doses of 150–450 x 106 CAR+ T cells in RRMM patients after a median of **6 prior lines of therapy (84% TCR)**

Led to EMA approval of ide-cel for **TCE MM, ≥ 3 priorLOT**

Jagannath S et al, JCO 2025., Munshi NC, et al. N Engl J Med 2021;384:705-16

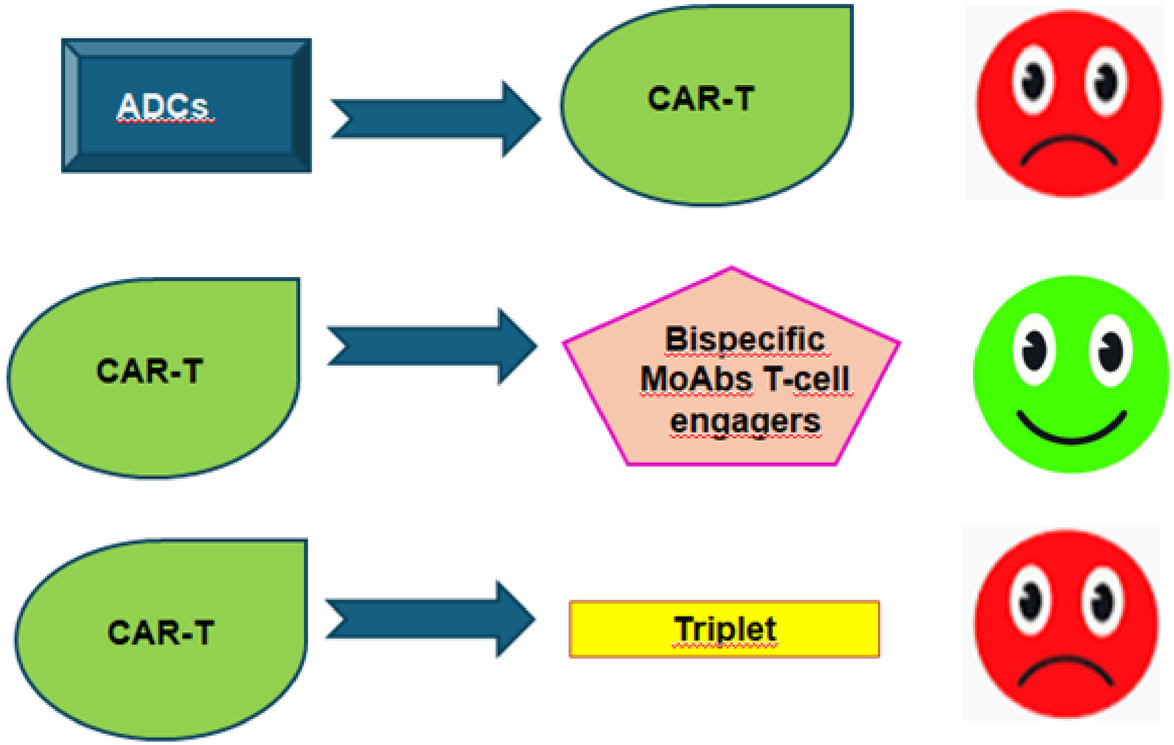
Use of immunotherapies in 2nd or more advanced relapses

	Anti-BCMA			Anti-GPRC5D
	Teclistamab	**Elranatamab**	**Linvoseltamab**	**Talquetamab**
Registrational trial	MajesTEC-1	MagnetisMM -3	Linker-MM1	MonumenTAL- 1
N°, pts	165	123	117	288 (143: 0.4 mg/kg / 145: 0.8 mg/kg)
Median F-up (months)	30.4	28.4	14.3	31.2
Median prior LOT (months)	5	5	5	5/5
ORR	63%	61%	71%	74/69%
Median PFS (months)	11.3	17.2	NR*(89% at 12 mths)	7.5/11.2

Linvoseltamab non è rimborsato per il trattamento del Mieloma Multiplo RR

Use of immunotherapies in 2nd or more advanced relapses

Sequencing of the immunotherapies in patients with RRMM presents challenges; further prospective studies will provide more insights into this important issue. Currently available data suggest that CAR T cell therapies might need to be given to eligible patients before BCMA-targeted ADCs or bispecific T cell engagers [panel consensus; III, B]. Bispecific T cell engagers can be effective immediately after disease progression on CAR T cells, and talquetamab is possibly the agent with better outcomes in this setting



mPFS: 4 months for idecel, 9.5 months for ciltacel (but 5.3 months if prior moAbs T-cell engager)

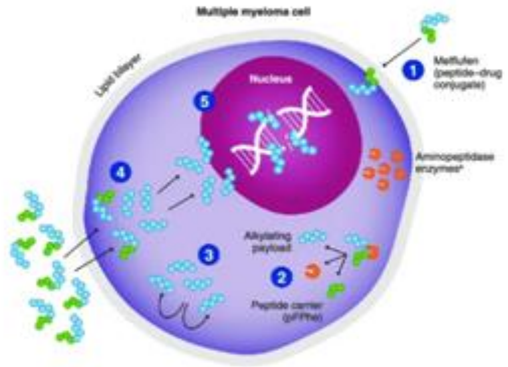
ORR
Teclistamab 64%
Talquetamab 79%

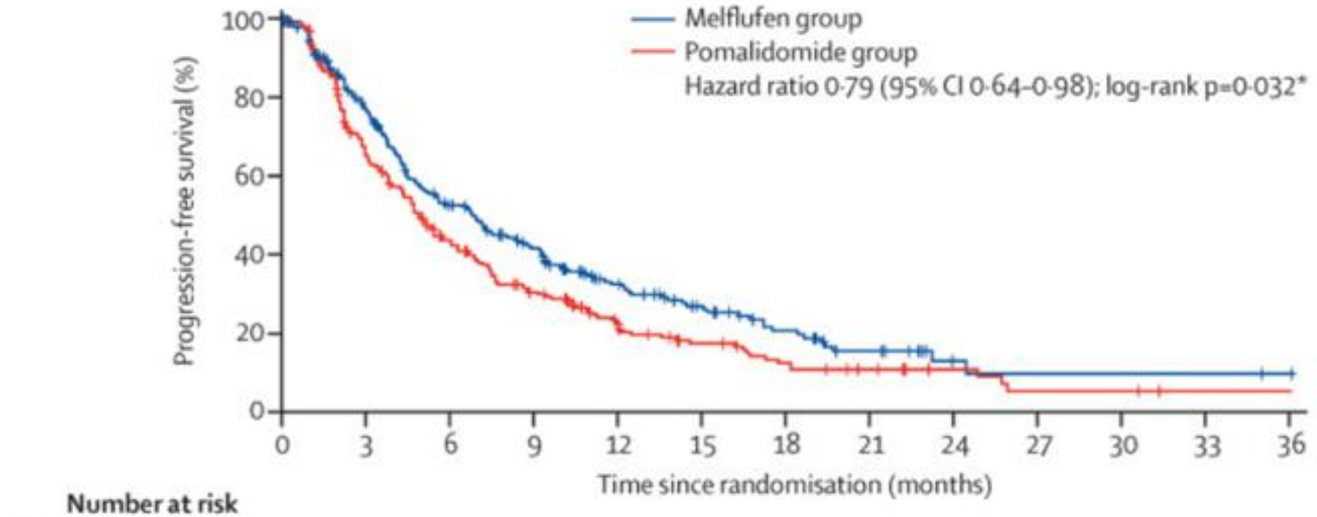
ORR 30%, no CR

Ferreri CJ et al. Blood Cancer J, 2023, Merz M et al. Blood Cancer J, 2024

2nd or more advanced relapse

Patients with triple-class refractory MM can receive cilta-cel or ide-cel in the third or fourth lines of treatment [I, A] or in the fifth line and beyond [II, B], teclistamab [II, B], elranatamab [II, B], linvoseltamab [II, B], talquetamab [II, B] or BelaPd [I, A]. These patients can also receive melflufen if they had not previously undergone ASCT or if the time to disease progression after ASCT is ≥3 years [I, B]. Seld is another option in these patients [II, B].





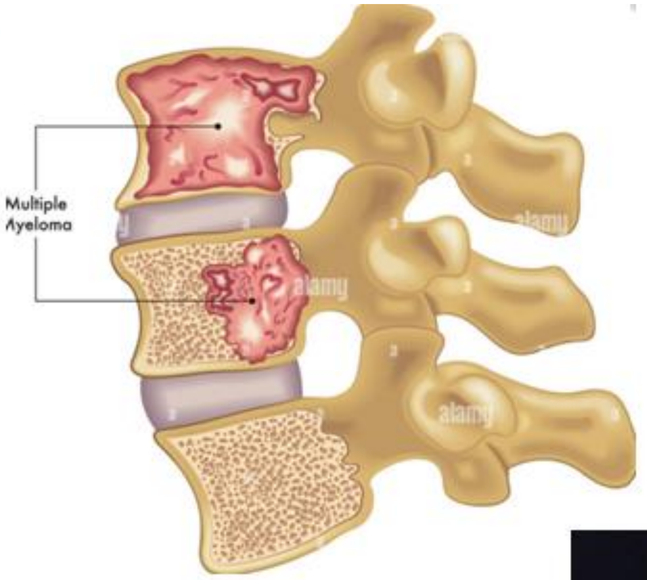
Number at risk (number censored)													
Melflufen group	246	168	109	80	50	34	22	13	5	3	3	3	2
	(0)	(25)	(32)	(39)	(53)	(61)	(66)	(70)	(77)	(78)	(78)	(78)	(79)
Pomalidomide group	249	150	90	58	37	23	15	10	6	3	3	1	1
	(0)	(16)	(26)	(33)	(41)	(47)	(49)	(52)	(56)	(56)	(56)	(58)	(58)

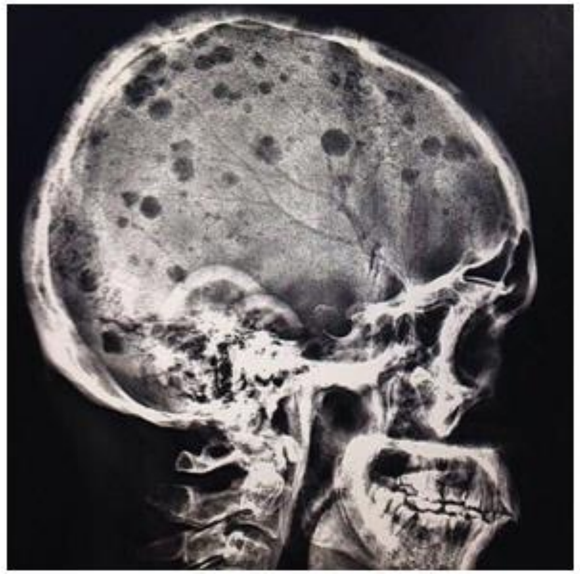
AIFA approved: RRMM 4L+, triple class refractory. No ASCT o ASCT with Time to Progression(TTP) ≥36 mesi.

Schjesvold et al. Lancet 2022

Supportive care - How to manage old and new toxicities, bone lesions

- Antiresorptive agents should be given in addition to myeloma-directed therapy in all patients with MM and osteolytic disease at diagnosis [I, A].
- Denosumab is a reasonable option in patients with severe renal impairment, in whom aminobisphosphonates are not recommended; caution is needed owing to a high risk of hypocalcaemia [III, C].
- Zoledronic acid should be given monthly in patients with suboptimal response (PR or less) and at least for 4 years [I, A].
- In patients who have a CR or vgPR, 12–48 months of therapy with zoledronic acid seems adequate. At relapse, zoledronic acid should be reinitiated [III, B].
- Denosumab should be given every 4 weeks continuously. Discontinuation of denosumab is challenging owing to the lack of data on how to stop denosumab in patients with MM; until these data are available, discontinuation of denosumab must be followed by a dose of zoledronic acid (6–9 months after the last dose of denosumab) to prevent any 'rebound' phenomenon [III, B].
- Vitamin D and calcium supplementation is mandatory when administering either bisphosphonates or denosumab [I, A].
- Low-dose radiation therapy (up to 30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathological fracture, or for impending spinal cord compression [II, A].
- Balloon kyphoplasty should be considered for symptomatic vertebral compression fractures with refractory pain [II, B].
- Surgery is recommended for long-bone fractures, bony compression of the spinal cord, or vertebral column instability [II, A].





Dimopoulos MA et al. Nat Rev Clin Oncol, 2025

Supportive care - How to manage old and new toxicities
Renal impairment

- Bortezomib-based regimens remain the cornerstone of the management of MM-related renal impairment [I, A].
- High-dose dexamethasone at least for the first month of therapy [II, B].
- Patients eligible for ASCT can receive DaraVTd or DaraVCd [II, B]. If reversal of renal impairment is observed, thalidomide or cyclophosphamide might be substituted by lenalidomide [panel consensus; V, B]. In patients who are ineligible for ASCT, DaraVCd or VMP can also be administered [II, B] but no data on this regimen in patients undergoing dialysis are available.
- Pomalidomide, carfilzomib, ixazomib, daratumumab and isatuximab need no dose modifications in patients with renal impairment [II, B].
- CAR T cells can be given in patients with mild to moderate renal impairment [II, B].
- Teclistamab can be given to patients with MM-related renal impairment, even including those undergoing dialysis [III, C].

Dimopoulos MA et al. Nat Rev Clin Oncol, 2025

Supportive care - How to manage old and new toxicities
Infections

- Immediate therapy with broad-spectrum antibiotics [I, A].
- Prophylactic antibiotics (such as levofloxacin) for the first 3 months of initiation of therapy, especially in patients receiving lenalidomide or pomalidomide, or in those at high risk of infections [I, A].
- Sulfamethoxazole and trimethoprim are recommended for the prevention of *Pneumocystis jirovecii* infection [I, A].
- Acyclovir or valacyclovir for herpes zoster prophylaxis is recommended in patients receiving proteasome inhibitors, anti-CD38 antibodies and BCMA-targeted therapies [II, A].
- Vaccination for influenza, varicella zoster (inactivated vaccine), SARS-CoV-2 and pneumococcal infections [II, A] as well as for respiratory syncytial virus [III, C].
- Intravenous IgG prophylaxis is not routinely recommended although it is highly recommended in patients receiving either bispecific T cell engagers or CAR T cells [III, C]; it should be used in patients with low IgG levels (<400–500 mg) and in those with at least two severe infections requiring hospitalization during the previous year [II, B].

Dimopoulos MA et al. Nat Rev Clin Oncol, 2025

Supportive care - How to manage new toxicities, CRS – ICANS, ocular toxicity

Box 3 | Summary of recommendations for the management of toxicities derived from novel therapies in patients with multiple myeloma

CRS

Grade 1
- Supportive care including analgesics and antipyretics [I, A].
- If fever persists, check for infections [I, A].
- Consider tocilizumab for persistent (>3 days) and refractory fever [I, A].

Grade 2
- Intravenous fluid bolus [I, A].
- Tocilizumab early if fever of ≥39°C persists, if hypotension persists despite the use of initial fluid bolus or after initiation of oxygen supplementation [II, B].
- If hypotension persists after a second fluid bolus and tocilizumab, transfer to the intensive care unit [I, A].
- Add dexamethasone if hypotension persists after anti-IL-6 antibodies, high risk of severe CRS, worsening hypoxia or clinical concern [panel consensus, IV, C].

Grade 3
- Consider intensive care [I, A].
- Administer tocilizumab [II, B].
- Add dexamethasone if no response within 24 h, increasing dose if refractory [II, B].
- Add anakinra if CRS unresponsive [panel consensus; III, C].
- Consider etanercept as clinically appropriate [panel consensus; III, C].

Grade 4
- Consider intensive care [I, A].
- Administer tocilizumab [II, B].
- Administer high-dose methylprednisolone [II, B].
- Add anakinra if CRS unresponsive [panel consensus; III, C].
- If CRS remains unresponsive consider alternative agents such as etanercept [panel consensus; III, C].

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Grade 1
- Observation.
- Withhold oral food, medicine and fluid intake and switch to intravenous intake.
- Haloperidol or lorazepam if patient is agitated [II, B].
- Consider early dexamethasone in high-risk patients [II, B].
- Start non-sedating AEDs if not already being administered [panel consensus; III, C].
- MRI of brain, lumbar puncture, funduscopic examination and/or EEG [I, A].

Grade 2
- Dexamethasone [II, B].
- If no improvement after 48 h, increase dexamethasone dose or administer alternative agents such as anakinra or tocilizumab in the concomitant presence of CRS [II, B].
- Start non-sedating AEDs if not already being administered [II, B].
- Consider EEG and CT or MRI [II, B].

Grade 3
- Dexamethasone [II, B].
- If no improvement after 24 h, increase dexamethasone dose [II, B], or administer high-dose methylprednisolone and/or alternative agents such as anakinra [panel consensus; IV, C].
- Start non-sedating AEDs if not already being administered [II, B].
- Consider EEG and CT or MRI [II, B].
- Acetazolamide if increased CSF pressure [panel consensus; IV, C].

Grade 4
- Dexamethasone [II, B].
- If refractory, administer high-dose methylprednisolone [panel consensus; IV, C].
- If ICANs remains refractory, consider alternative therapies including lymphodepletion with cyclophosphamide or other drugs [panel consensus; IV, C].
- Consider mechanical ventilation, EEG and CT or MRI [II, B].
- Drain CSF if increased CSF pressure [panel consensus; V, C].

Ocular toxicities

- Ophthalmology evaluation is recommended before each belantamab mafodotin infusion for the first four cycles [I, A].
- The treating physician can decide for the next dose administration or delay based on the vision-related anamnestic tool [II, B].
- Dose delays, dose reductions and prolonged intervals (every 8 to 12 weeks) between belantamab mafodotin administration lead to the recovery of ocular AEs without affecting the efficacy of the drug [I, A].

Dimopoulos MA et al. Nat Rev Clin Oncol, 2025

Conclusion

The new EHA-EMN guidelines are the new “state of the art” of the management of MM patients and are based on treatments approved, or in the process of approval, by the EMA. New treatments are included extensively.

Compared to the 2021 guidelines, the decision-making architecture changes drastically, especially for risk stratification, use of MRD, intensity of the first line and early placement of immunotherapies in relapses.

Therapeutic sequencing is renewed. In 2021, the sequencing was still dominated by "what the patient has already received" within the three traditional major classes; in 2025, the issue becomes "which immunological target has already been used, for how long, with what refractoriness, and with what window for withdrawal or target change.”

Regarding complications and supportive care, 2021 remained firmly anchored to the traditional recommendations for bone, infections, anemia, kidney, and thrombosis. 2025 guidelines substantially update them to address new toxicities. The new 2025 guidelines draw the attention on the clinical infrastructure needed to safely administer those drugs.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