Lymphoma · Leukemia & Myeloma Congress

Management of The Frail and Transplant-Ineligible Patient

María-Victoria Mateos

University Hospital of Salamanca, Spain

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lymphomaandmyeloma.com

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Disclosures

- Honoraria derived from lectures and participation in advisory boards from AbbVie, Amgen, Celgene, GSK, Janssen, Oncopeptides, Pfizer, Regeneron, Roche, Sanofi, Stemline, Takeda

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Learning Objectives

- Evaluate the clinical efficacy and safety data surrounding new and emerging therapeutics to develop treatment algorithms for patients with newly-diagnosed MM
- Assess barriers to optimal treatment including the therapeutic implications of combination regimens in the management of patients with MM
- Discuss challenges related to current MM management paradigms to decrease the risk of treatment associated AEs, improve therapeutic resistance
- Consider factors which impact treatment selection in transplant-ineligible/frail patients with multiple myeloma

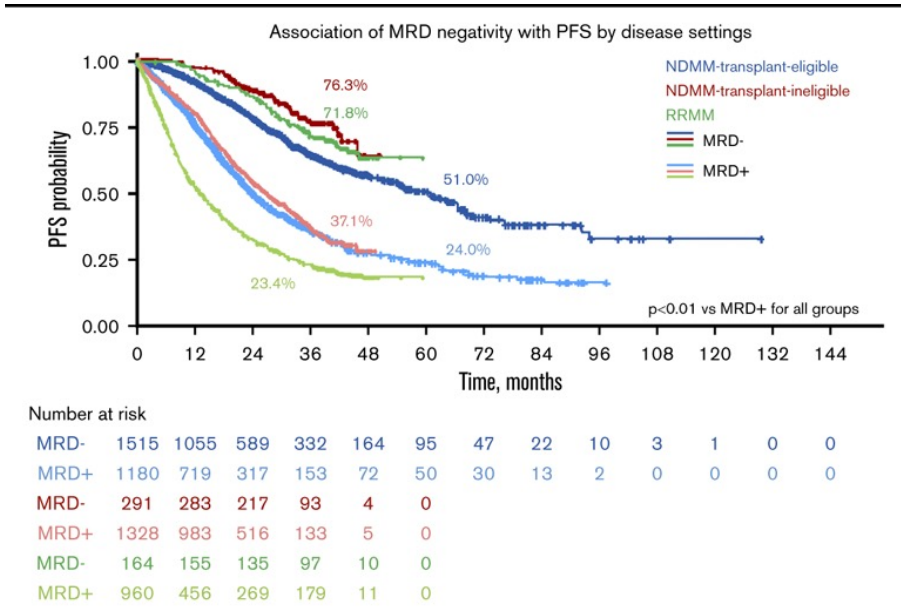
What Should the Optimal Treatment Goals Be for These NDMM Patients?

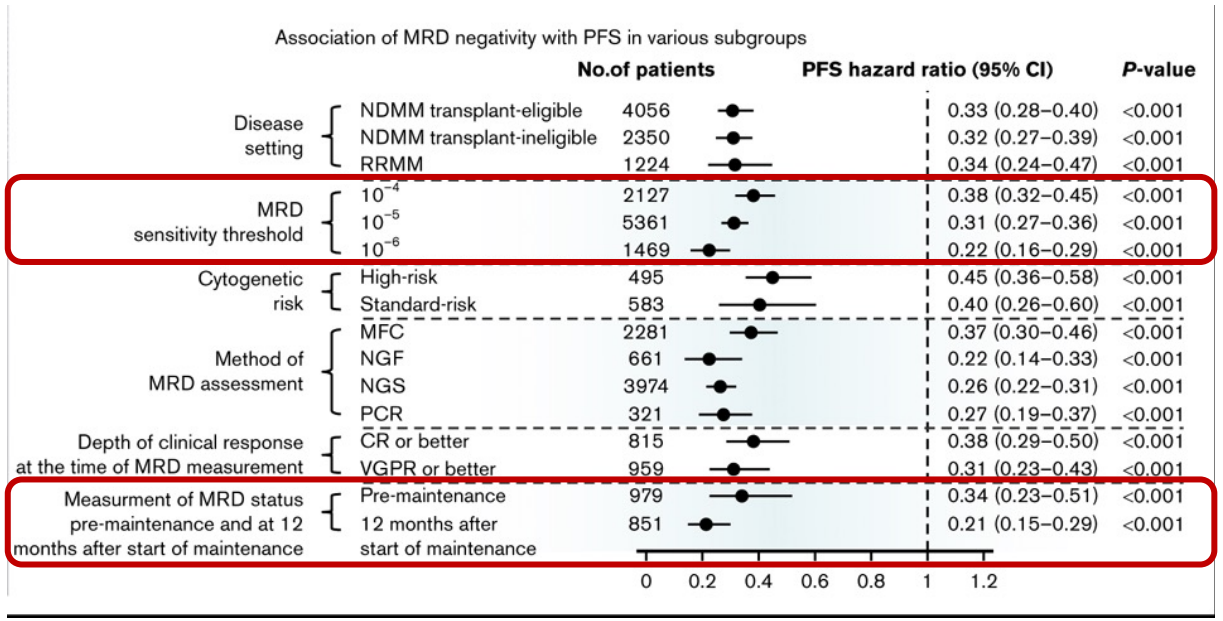
- To achieve long-term survival with good quality of life
- Prolong survival
- Delay disease progression
- Ensure good quality of life

To achieve these goals..... eradication or at least major reduction of the tumor clone is required

NDMM = newly diagnosed multiple myeloma.
Mateos MV. Personal communication.

MRD as Prognostic across MM Patients Subgroups

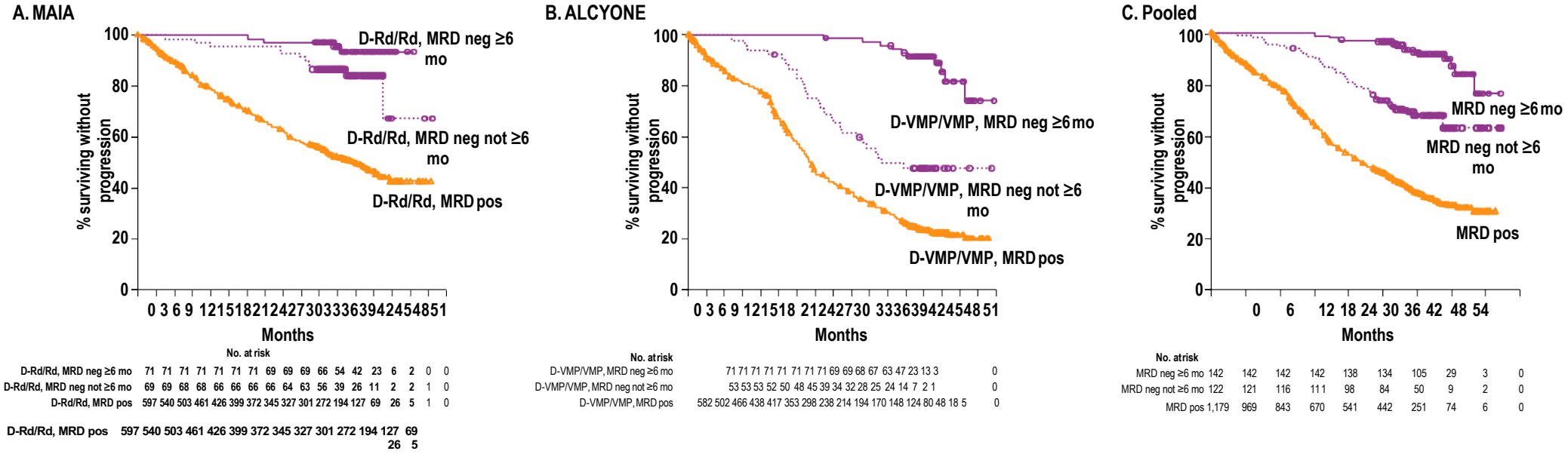




CI, confidence interval; MRD, minimal residual disease; NDMM, newly-diagnosed multiple myeloma; PFS, progression free survival; RRMM, relapsed refractory multiple myeloma.

Munshi N, et al. *Blood Adv.* 2020;4(23):5988-5999.

PFS Based on Sustained MRD Negativity (NGS, 10^{-5}) Lasting ≥6-12 Months in MAIA (A), ALCYONE (B), and in Both Studies Pooled (C)



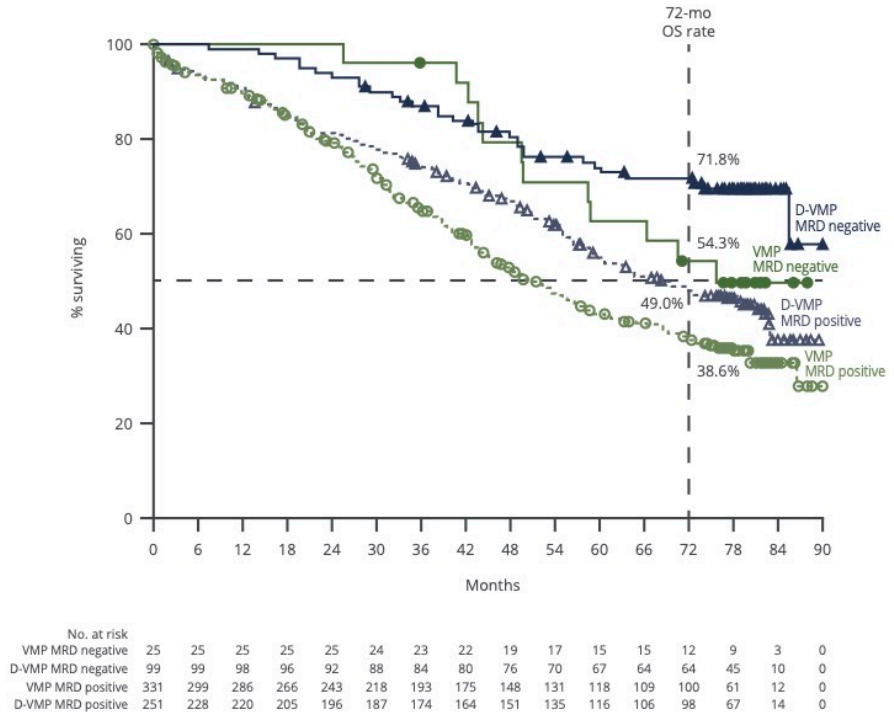
Both in MAIA and ALCYONE individually, as well as in the pooled analysis, durable MRD negativity lasting ≥6 months improved PFS compared with MRD-negative patients who did not maintain MRD negativity for ≥6 months

San-Miguel J, et al. *Blood.* 2022;139(4):492-501.

ALCYONE: DVMP vs VMP: OS by MRD status

MRD by NGS 10^{-5}	D-VMP (n = 350)	VMP (n = 356)	*P* value
MRD negative, n (%)	99 (28.3)	25 (7.0)	<0.0001
Sustained MRD negative, n (%)			
Lasting ≥12 months	49 (14.0)	10 (2.8)	<0.0001
Lasting ≥18 months	31 (8.9)	6 (1.7)	<0.0001

OS by MRD (NGS, 10^{-5})



D-, daratumumab; NGS, next-generation sequencing; PFS, progression-free survival; OS, overall survival; VMP, bortezomib, melphalan, prednisone.

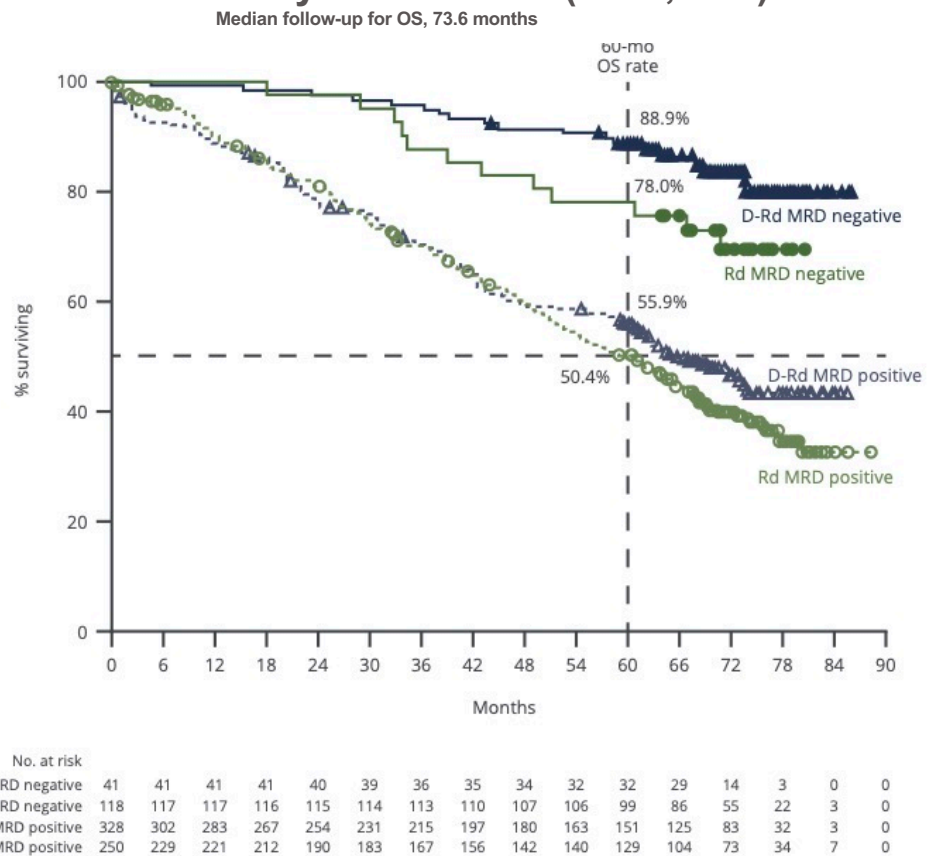
Mateos MV, et al. Presented at: ASH;2022. Abstract 4561.

MAIA Updated Analysis: DRd vs Rd: OS by MRD Status

Summary of ORR and MRD-negativity rates (NGS, 10^{-5})

	D-Rd (n = 368)	Rd (n = 369)	*P* value
Response, n (%)			
ORR	342 (92.9)	301 (81.6)	<0.0001
≥CR	188 (51.1)	111 (30.1)	<0.0001
sCR	131 (35.6)	58 (15.7)	<0.0001
CR	57 (15.5)	53 (14.4)	
≥VGPR	300 (81.5)	210 (56.9)	<0.0001
VGPR	112 (30.4)	99 (26.8)	
PR	42 (11.4)	91 (24.7)	
MRD negative, n (%)	118 (32.1)	41 (11.1)	<0.0001
Sustained MRD negative, n (%)			
Lasting ≥12 months	69 (18.8)	15 (4.1)	<0.0001
Lasting ≥18 months	62 (16.8)	12 (3.3)	<0.0001

OS by MRD status (NGS, 10^{-5})



CR, complete response; D-, daratumumab; NGS, next-generation sequencing; NR, not reached; OS, overall survival; PFS, progression-free survival; VMP, bortezomib, melphalan, prednisone.

Kumar S et al. Presented at: ASH;2022. Abstract 4559.

Attrition Rates by Subsequent Lines of Therapy in Patients with NDMM

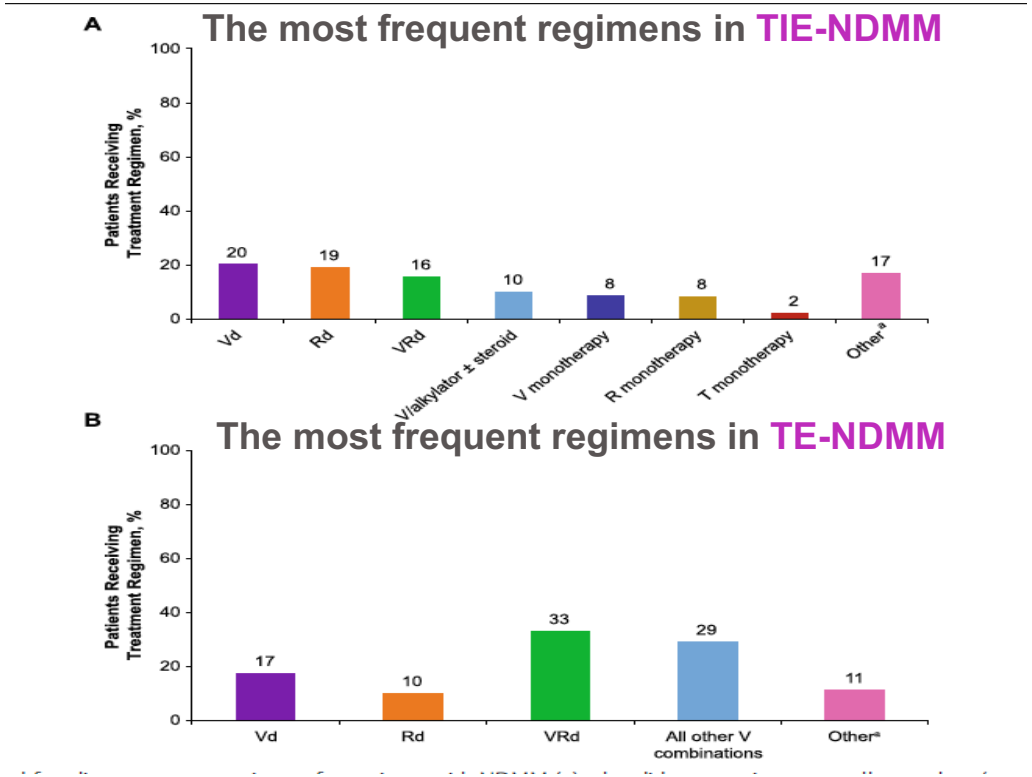


Table 4 Attrition rates by LOT

LOT	Frequency, *N*	Attrition, %	Deaths, *n* (%)	No subsequent treatment in follow-up, *n* (%)	Subsequent treatment, *n* (%)	Mean ± SD treatment duration, months (median)
Non-transplant						
1	22,062	–	2841 (12.9)	9716 (44.0)	9505 (43.1)	6.9 ± 9.6 (3.6)
2	9505	56.9	1155 (12.2)	3168 (33.3)	5182 (54.5)	7.5 ± 9.5 (4.1)
3	5182	45.5	636 (12.3)	1575 (30.3)	2971 (57.3)	6.5 ± 8.0 (3.7)
4	2971	42.7	364 (12.3)	901 (30.3)	1706 (57.4)	5.7 ± 6.6 (3.4)
5	1706	42.6	209 (12.3)	508 (29.8)	989 (58.0)	5.5 ± 6.4 (3.2)
Transplant						
1	2763	–	36 (1.3)	543 (19.6)	2184 (79.0)	6.3 ± 8.0 (4.2)
2	2184	21.0	60 (2.7)	613 (28.1)	1511 (69.2)	6.1 ± 9.2 (2.7)
3	1511	30.8	63 (4.2)	494 (32.7)	954 (63.1)	7.4 ± 9.8 (3.6)
4	954	36.9	60 (6.3)	276 (28.9)	618 (64.8)	6.6 ± 9.4 (3.4)
5	618	35.2	49 (7.9)	180 (29.1)	389 (62.9)	5.6 ± 6.2 (3.3)

LOT Line of therapy, *SD* Standard deviation

High attrition rates underscore the need to use the most optimal treatment regimens upfront better than reserving them for later LOTs in which the clinical benefit may decrease

Fonseca R, et al. *BMC Cancer.* 2020(20):1087.

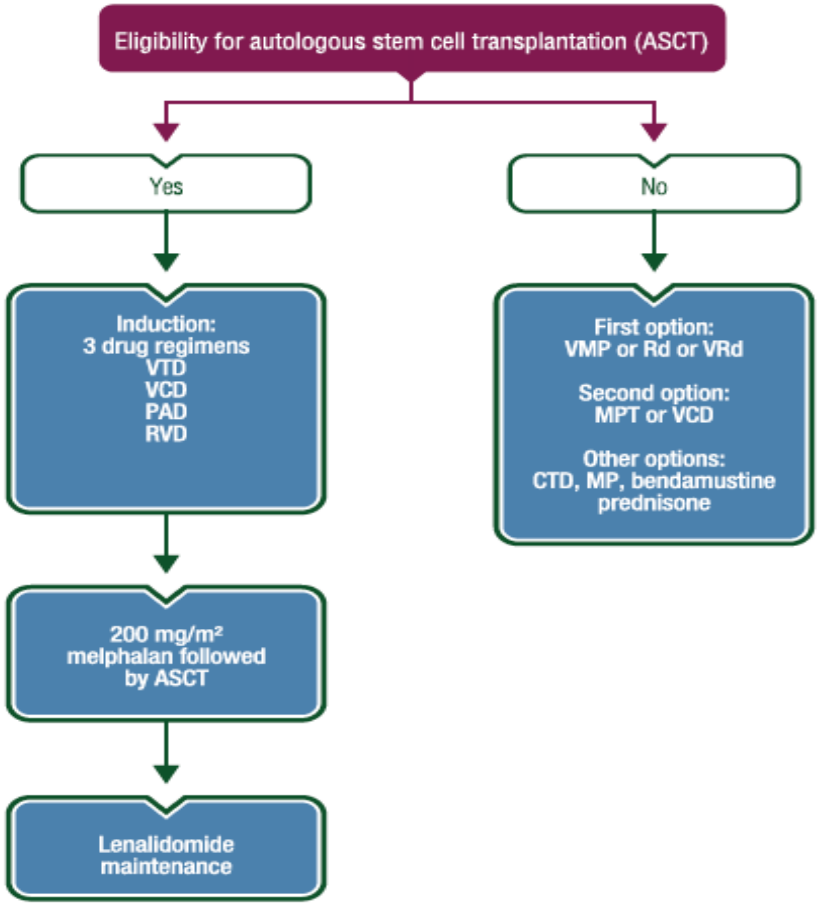
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

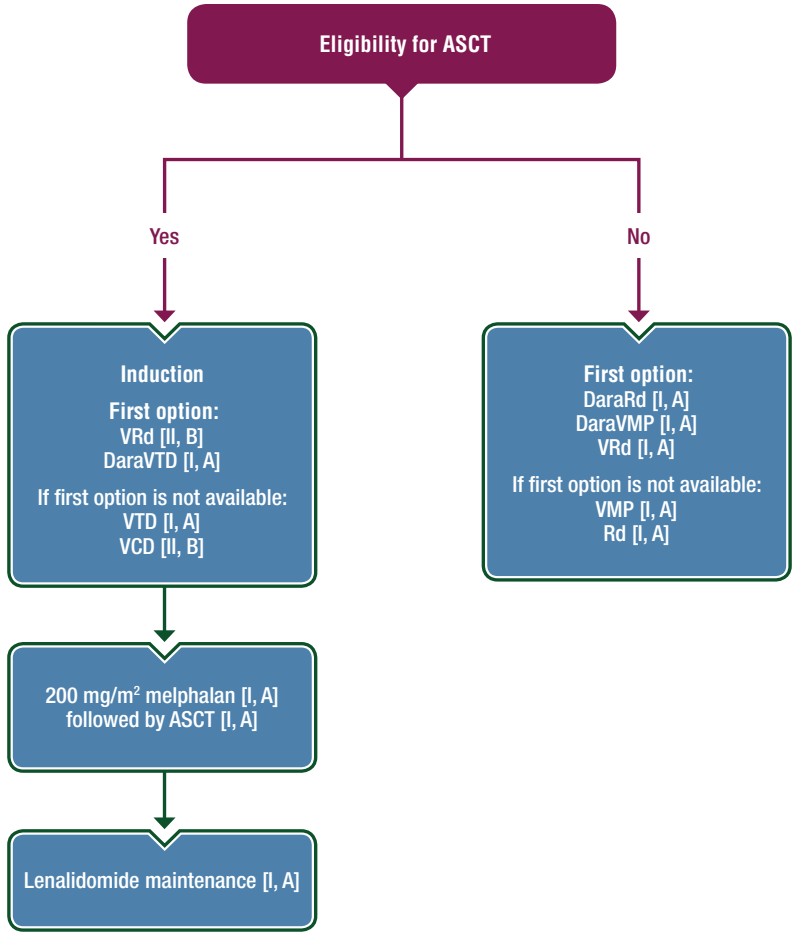
CLINICAL PRACTICE GUIDELINES

Annals of Oncology 28 (Supplement 4): iv52–iv61, 2017
doi:10.1093/annonc/mdx096
Published online 27 April 2017

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

P. Moreau[1], J. San Miguel[2], P. Sonneveld[3], M. V. Mateos[4], E. Zamagni[5], H. Avet-Loiseau[6], R. Hajek[7], M. A. Dimopoulos[8], H. Ludwig[9], H. Einsele[10], S. Zweegman[11], T. Facon[12], M. Cavo[5], E. Terpos[8], H. Goldschmidt[13], M. Attal[6] & C. Buske[14], on behalf of the ESMO Guidelines Committee*

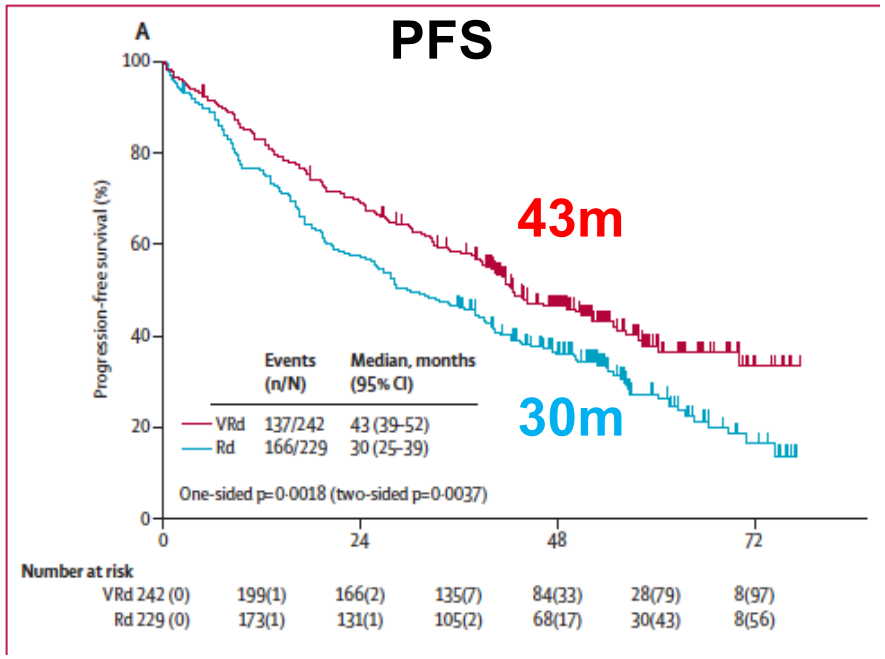


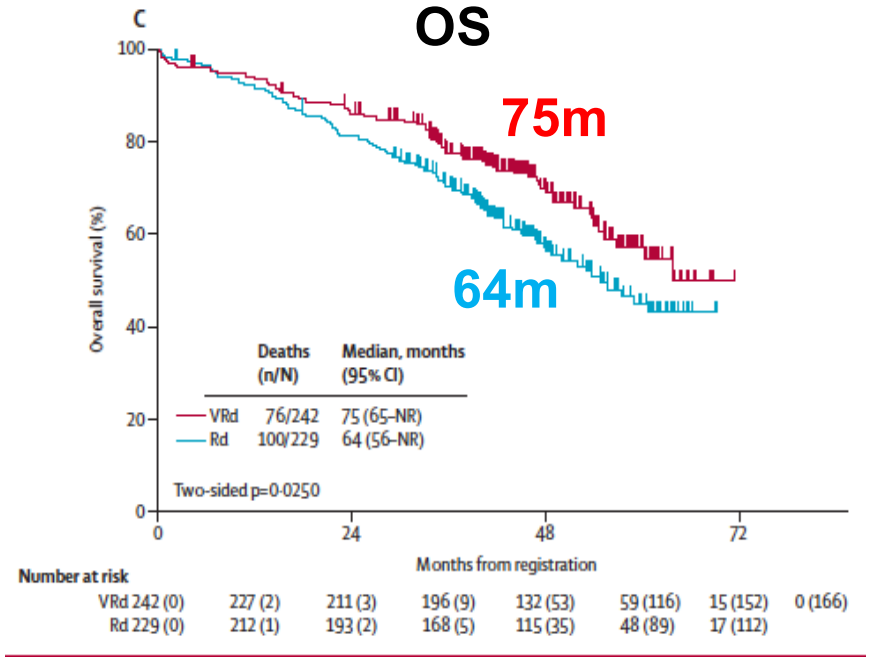


SWOG: VRd-->Rd vs Continuous Rd

Bortezomib twice a week IV x 8 cycles

ORR (CR) (%): 81(22) vs 71(8)





G3-4 AEs: PN (33%)

Durie BGM, et al. *Lancet.* 2017;389(10068):519-527.

SWOG: VRd-->Rd vs Continuous Rd

Bortezomib twice a week IV x 8 cycles

ORR (CR) (%): 81(22) vs 71(8)

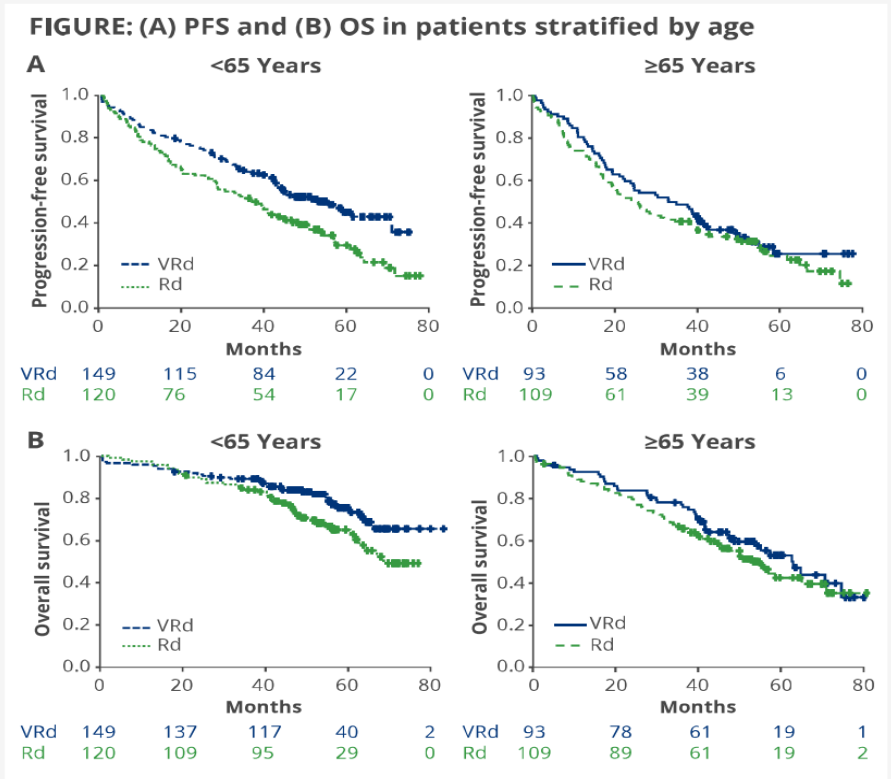


TABLE 2: Age-stratified analyses of PFS, OS, and safety

	Outcome	Age <65 years (n=269)		Age ≥65 years (n=202)	
		VRd (n=149)	Rd (n=120)	VRd (n=93)	Rd (n=109)
PFS	Median PFS, months	55.4	36.6	33.1	25.8
	HR (95% CI)	0.63 (0.46–0.87)		0.83 (0.60–1.16)	
	Adjusted HR[a] (95% CI)	0.61 (0.45–0.84)		0.90 (0.65–1.26)	
OS	Median OS, months	Not reached	68.9	62.9	53.0
	HR (95% CI)	0.61 (0.39–0.97)		0.83 (0.55–1.23)	
	Adjusted HR[a] (95% CI)	0.62 (0.39–0.99)		0.88 (0.59–1.31)	
Safety[b]	Grade ≥3 TEAE	87%	79%	93%	89%
	Treatment discontinuation due to toxicity	29%	18%	47%	26%

HRs are from Cox proportional hazard regressions with treatment arm as the explanatory variable. A HR <1 indicates advantage of VRd over Rd.
[a]Adjusted hazard ratio estimates reflect results from weighted Cox regression models where IPTW was used to balance the VRd and Rd trial arms on the following baseline characteristics within each age subgroup (≥65, <65 years): age, sex, ISS stage, ECOG PS score, hemoglobin (<10 g/dL, ≥10 g/dL), serum creatinine (<2 mg/dL, ≥2 mg/dL), cytogenetic risk by FISH test (high, intermediate, low, normal/missing/insufficient), and lactate dehydrogenase (<190 IU/L, ≥190 IU/L). Absolute standardized mean differences for all covariates were <0.1 with IPTW. [b]Eligible safety assessment population was n=467.
CI, confidence interval; FISH, fluorescence in situ hybridization; HR, hazard ratio; IPTW, inverse probability treatment weighting; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Durie B, et al. Presented at: ASH;2022. Abstract 4497.

Modified Lenalidomide, Bortezomib, and Dexamethasone in Transplant-Ineligible Multiple Myeloma (n=50 pts)

Induction (cycles 1-9)
Repeat q35 days × 9 cycles

Lenalidomide 15 mg po days 1-21
Bortezomib 1.3 mg/m^2 sc* days 1, 8, 15, 22
Dexamethasone 20 mg po days 1, 2, 8, 9, 15, 16, 22, 23 (patients ≤75 years)
Dexamethasone 20 mg po days 1, 8, 15, 22 (patients >75 years old)

↓

Consolidation (cycles 10-15)
Repeat q28 days × 6 cycles

Lenalidomide 15 po days 1-21 (or last tolerated dose as of cycle 9)
Bortezomib 1.3 mg/m^2 sc days 1, 15 (or last tolerated dose as of cycle 9)

* The first 10 patients received bortezomib intravenously for cycle 1 only followed by subcutaneous administration. Subsequent patients received bortezomib subcutaneously.

Maintenance with Len was allowed according to the investigator criteria **and 66% of patients received it**

Median f/u is 61 months

- Efficacy: 86% ORR with 66% of ≥ VGPR

Safety profile

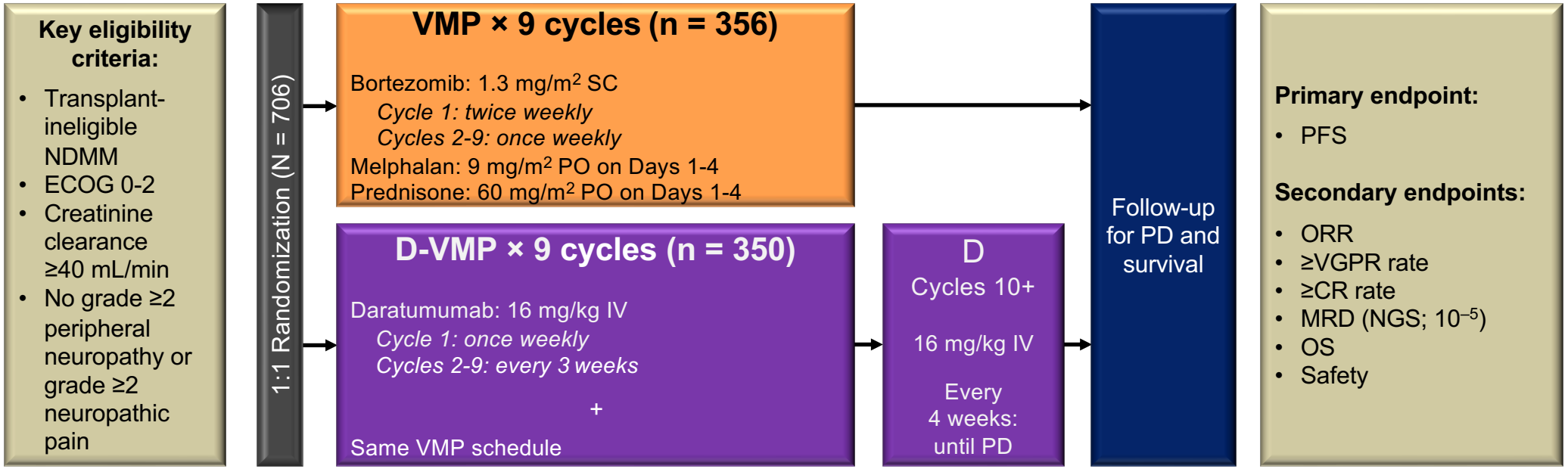
- Fatigue reported in 74% of patients and G3-4 in only 16%
- Neutropenia G34 in 14%
- Rash G34 in 10%
- PN G12 in 60%
- Patients reported improvement of their symptomatology with exception of diarrea

Median PFS = 42 months (95%CI 30.9 –

Median OS not reached with 61.3% of patients alive at 5 years

O'Donnell EK, et al. *Blood*. 2019;134(Suppl_1):3178.

ALCYONE Study Design



ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; SC, subcutaneously; PO, orally; IV, intravenously; D, daratumumab; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.

[a]8-month PFS improvement over 21-month median PFS of VMP.

Dimopoulos MA, et al. Presented at: ASH;2018. Abstract 156.

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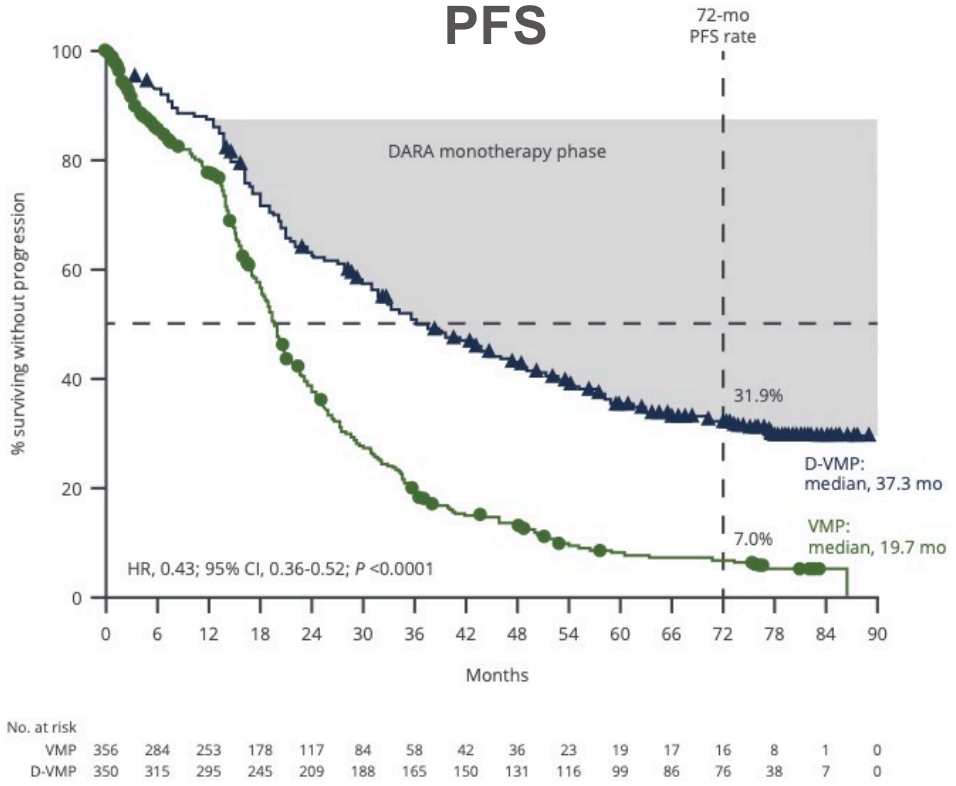
ALCYONE: PFS, OS and MRD

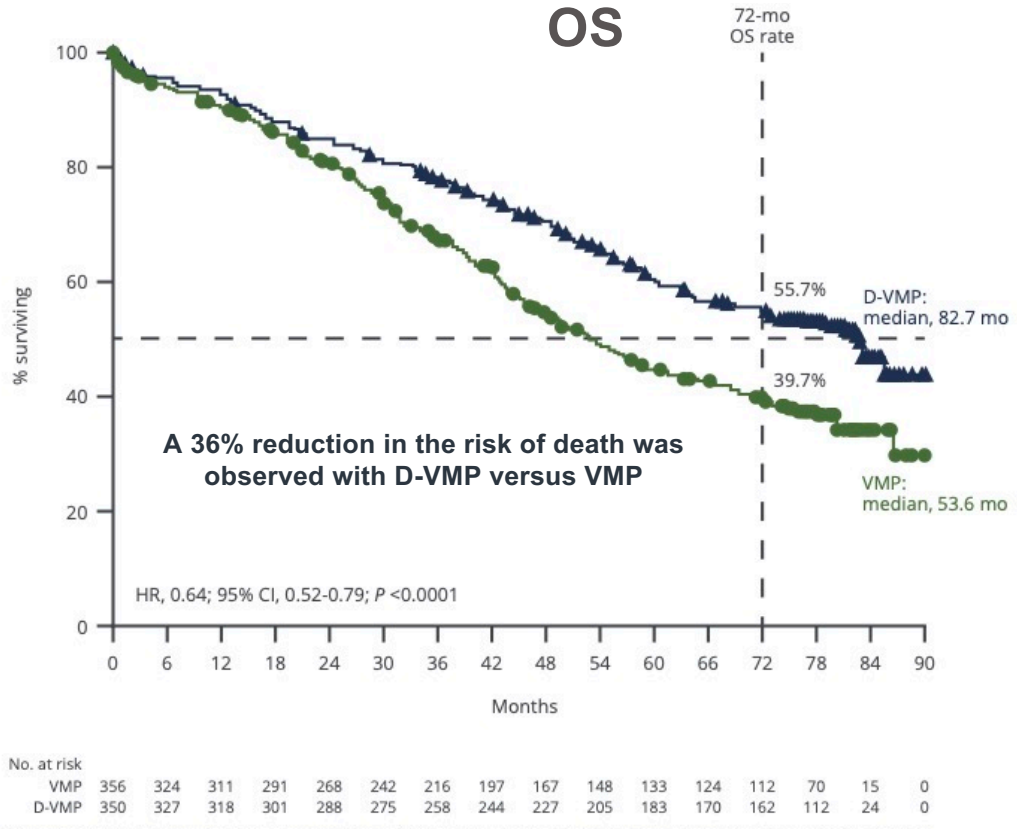
Median follow-up of 78.8 months

ORR: 91% vs 74% (SCR/CR rate: 46% vs 25%); MRD –ve rate: 28% vs 7%

PFS



OS



D-, daratumumab; PFS, progression-free survival; OS, overall survival; VMP, bortezomib, melphalan, prednisone.

ALCYONE: Safety Profile

TEAEs

	D-VMP (n = 346)		VMP (n = 354)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic, n (%)				
Neutropenia	175 (50.6)	140 (40.5)	186 (52.5)	138 (39.0)
Thrombocytopenia	173 (50.0)	120 (34.7)	190 (53.7)	134 (37.9)
Anemia	112 (32.4)	63 (18.2)	131 (37.0)	70 (19.8)
Leukopenia	47 (13.6)	28 (8.1)	53 (15.0)	30 (8.5)
Lymphopenia	39 (11.3)	27 (7.8)	36 (10.2)	22 (6.2)
Nonhematologic, n (%)				
Upper respiratory tract infection	107 (30.9)	8 (2.3)	50 (14.1)	6 (1.7)

- Grade 3/4 TEAEs occurred in 82.9% of patients in the D-VMP arm and 77.4% of patients in the VMP arm
- Grade 3/4 infection rates were 30.3% with D-VMP and 15.0% with VMP
- The most common serious TEAE in both arms was pneumonia (D-VMP, 14.7%; VMP, 3.7%)
- The rate of treatment discontinuation due to TEAEs was similar between the D-VMP arm (9.0%) and the VMP arm (9.3%)

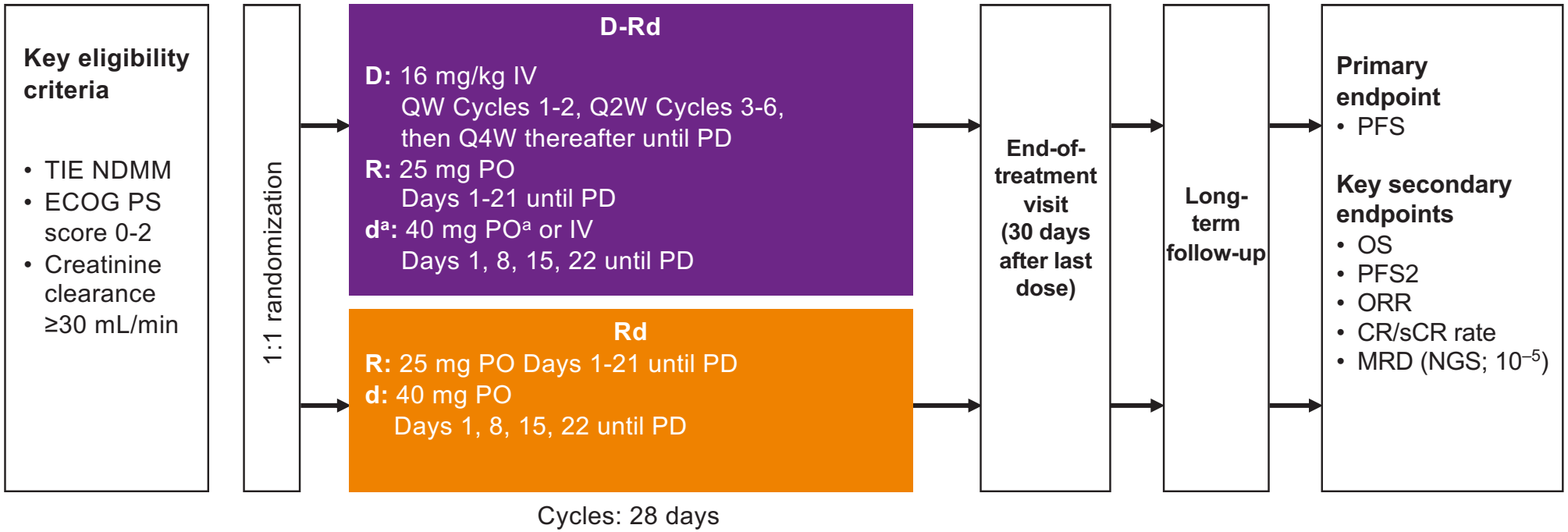
D-, daratumumab; PFS, progression-free survival; OS, overall survival; VMP, bortezomib, melphalan, prednisone.

TEAS = treatment-emergent adverse events.

Mateos MV, et al. Presented at: ASH;2022. Abstract 4561.

MAIA Study Design

- Multicentre, randomised, open-label, active-controlled, phase 3 study



[a]On days when daratumumab is administered, dexamethasone will be administered to patients in the D-Rd arm and will serve as the treatment dose of steroid for that day, as well as the required pre-infusion medication.

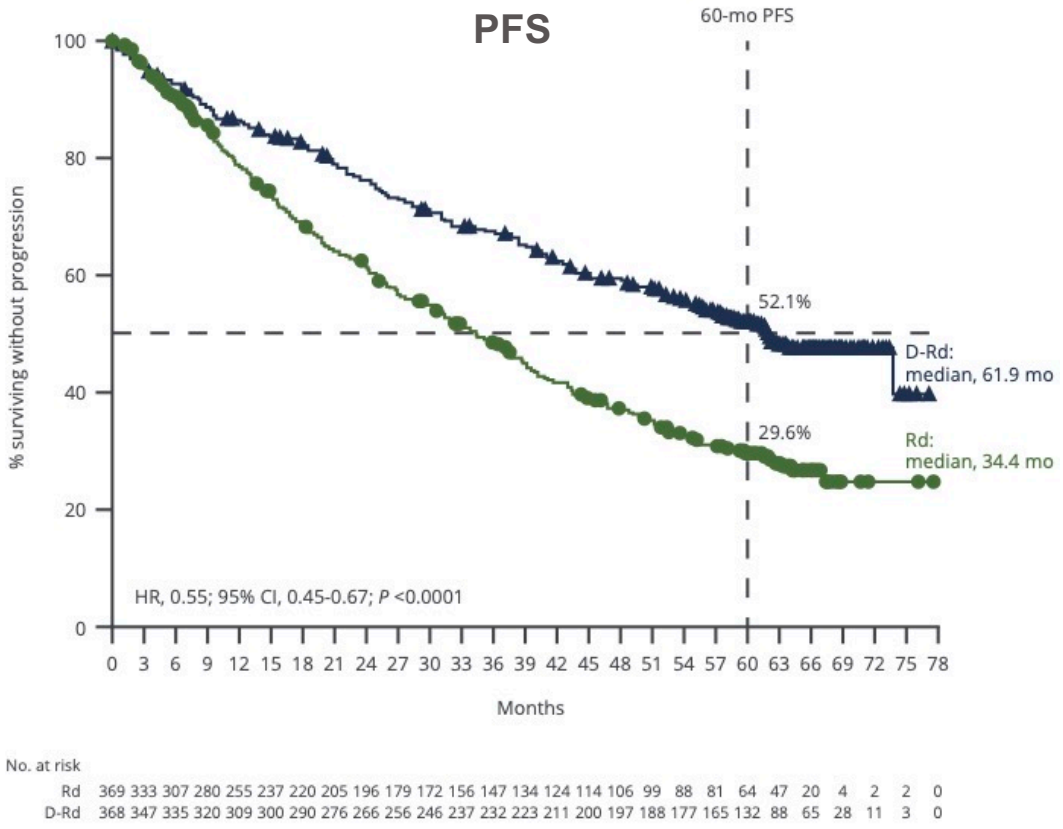
TIE, transplant-ineligible; NDMM, newly diagnosed multiple myeloma; ECOG PS, Eastern Cooperative Oncology Group performance status; D-Rd, daratumumab plus lenalidomide/dexamethasone; IV, intravenous; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; PO, oral; Rd, lenalidomide/dexamethasone; PFS, progression-free survival; CR, complete response; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; PFS2, progression-free survival on next subsequent line of therapy; OS, overall survival; ORR, overall response rate.

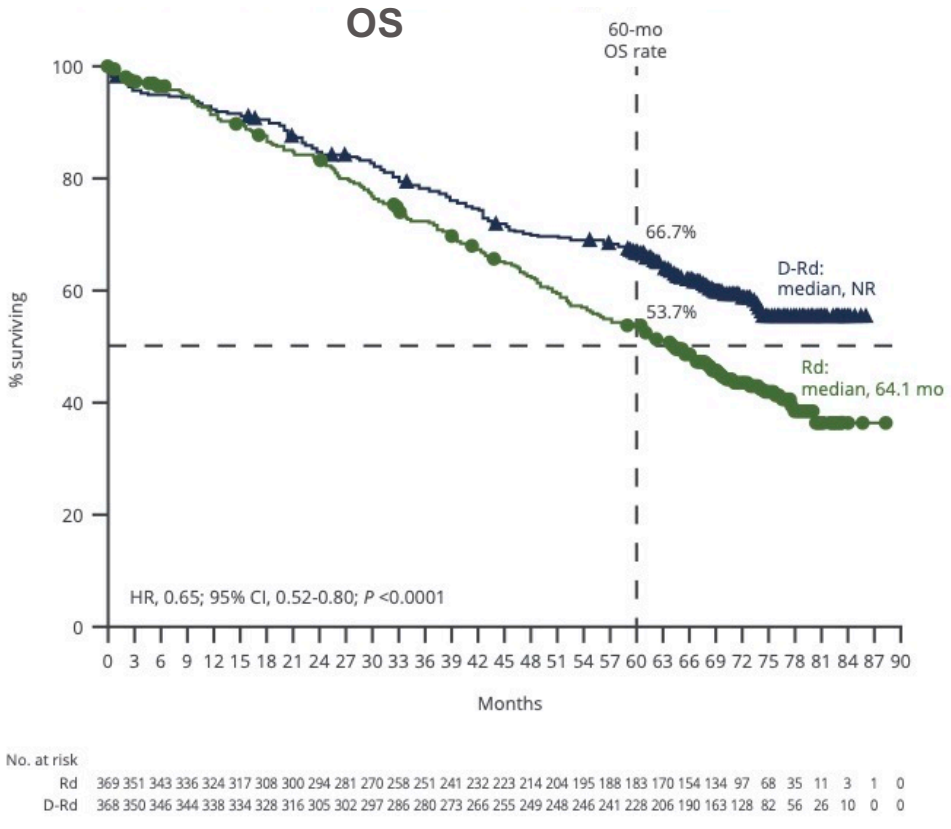
Kumar S, et al. Presented at: ASH;2022. Abstract 4559.
NCT02252172. Updated July 21, 2023. Accessed August 22, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT02252172.

MAIA Updated Analysis: PFS

Median follow-up of 64.5 months for PFS

ORR: 93% vs 82% (SCR/CR rate: 51% vs 30%); MRD –ve rate: 32% vs 11%





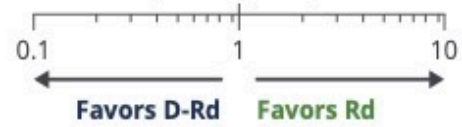
NR, not reached; OS, overall survival; PFS, progression-free survival; VMP, bortezomib, melphalan, prednisone.

Kumar S, et al. Presented at: ASH;2022. Abstract 4559.

MAIA Subgroups: Subgroup Analysis of PFS

Median follow-up of 64.5 months

	D-Rd		Rd		
	n/N	*Median PFS (mo)*	*n/N*	*Median PFS (mo)*	HR (95% CI)
ITT (overall)	176/368	61.9	228/369	34.4	0.55 (0.45-0.67)
Baseline characteristic					
Age ≥75 years	87/160	54.3	106/161	31.4	0.59 (0.44-0.79)
ISS stage III	61/107	42.4	73/110	24.2	0.61 (0.43-0.86)
Renal insufficiency	82/162	56.7	92/142	29.7	0.55 (0.41-0.75)
Extramedullary plasmacytomas	7/15	57.5	5/9	19.4	0.47 (0.15-1.50)
Cytogenetic risk					
Standard cytogenetic risk	126/271	63.8	174/279	34.4	0.51 (0.41-0.64)
High cytogenetic risk	28/48	45.3	31/44	29.6	0.57 (0.34-0.96)
Revised standard cytogenetic risk	78/176	NR	115/187	35.1	0.50 (0.37-0.66)
Revised high cytogenetic risk	82/156	56.0	96/152	30.7	0.59 (0.44-0.80)
Gain(1q21)	20/53	NR	28/44	37.8	0.43 (0.24-0.76)
Amp(1q21)	48/74	40.0	45/76	26.1	0.81 (0.54-1.21)
Gain(1q21) or amp(1q21)	68/127	53.2	73/120	32.3	0.63 (0.46-0.88)
1 HRCA	68/137	61.4	86/137	31.2	0.55 (0.40-0.76)
≥2 HRCAs	14/19	24.9	10/15	24.0	0.92 (0.40-2.10)
Isolated gain(1q21)	16/47	NR	27/42	37.8	0.36 (0.19-0.67)
Isolated amp(1q21)	38/61	42.8	38/65	28.9	0.78 (0.50-1.22)
Isolated gain(1q21) or amp(1q21)	54/108	61.4	65/107	37.1	0.58 (0.40-0.83)
Gain(1q21) or amp(1q21) plus ≥1 HRCA	14/19	24.9	8/13	24.0	1.03 (0.42-2.48)



D-Rd, daratumumab, lenalidomide, dexamethasone; HRCA, high risk cytogenetic abnormalities; ISS, International Staging System; PFS, progression-free survival; Rd, lenalidomide, dexamethasone.

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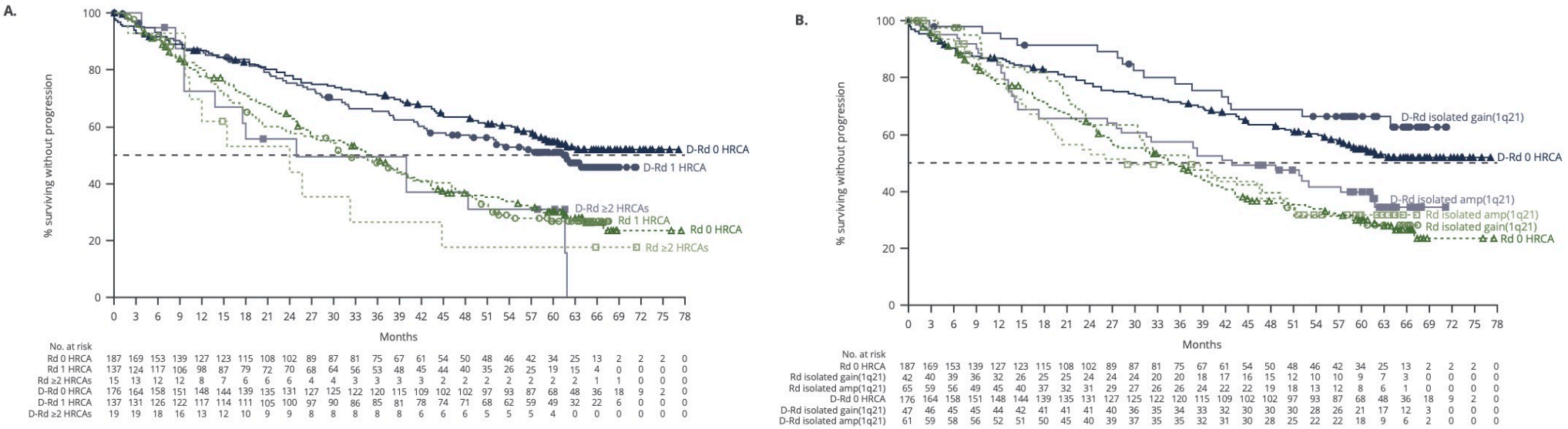
MAIA Cytogenetic Risk Subgroups: PFS

Median follow-up of 64.5 months

Subgroup analysis of PFS among (A) patients with revised standard cytogenetic risk (0 HRCA), 1 HRCA, or ≥2 HRCAs and (B) among patients with 0 HRCA, isolated gain (1q21), or isolated amp(1q21)



D-Rd, daratumumab, lenalidomide, dexamethasone; HRCA, high risk cytogenetic abnormalities; PFS, progression-free survival; Rd, lenalidomide, dexamethasone.

Moreau P, et al. Presented at: ASH;2022. Abstract 3245.

MAIA Updated Analysis: Subsequent Therapy and Safety

Subsequent therapy

- 128 patients in the D-Rd arm and 194 patients in the Rd arm received subsequent therapy
- Among patients who received subsequent therapy:
  - 9.4% of patients in the D-Rd arm and 23.2% of patients the Rd arm received a DARA-containing treatment as first subsequent therapy
- 14.1% of patients in the D-Rd arm and 48.5% of patients in the Rd arm received a DARA-containing treatment in any subsequent line of therapy

Safety profile

	D-Rd (n = 364)		Rd (n = 365)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic, n (%)				
Neutropenia	224 (61.5)	197 (54.1)	166 (45.5)	135 (37.0)
Anemia	154 (42.3)	62 (17.0)	150 (41.1)	79 (21.6)

- Grade 3/4 infection rates were 42.6% with D-Rd and 29.6% with Rd
- The most common serious TEAE in both arms was pneumonia (D-Rd, 18.7%; Rd, 10.7%)
- The rate of treatment discontinuation due to TEAEs was lower in the D-Rd arm (14.6%) versus the Rd arm (23.8%)

CR, complete response; D-, daratumumab; MRD, minimal residual disease; NGS, next-generation sequencing; NR, not reached; OS, overall survival; PFS, progression-free survival; VMP, bortezomib, melphalan, prednisone.

Kumar S, et al. Presented at: ASH;2022. Abstract 455.

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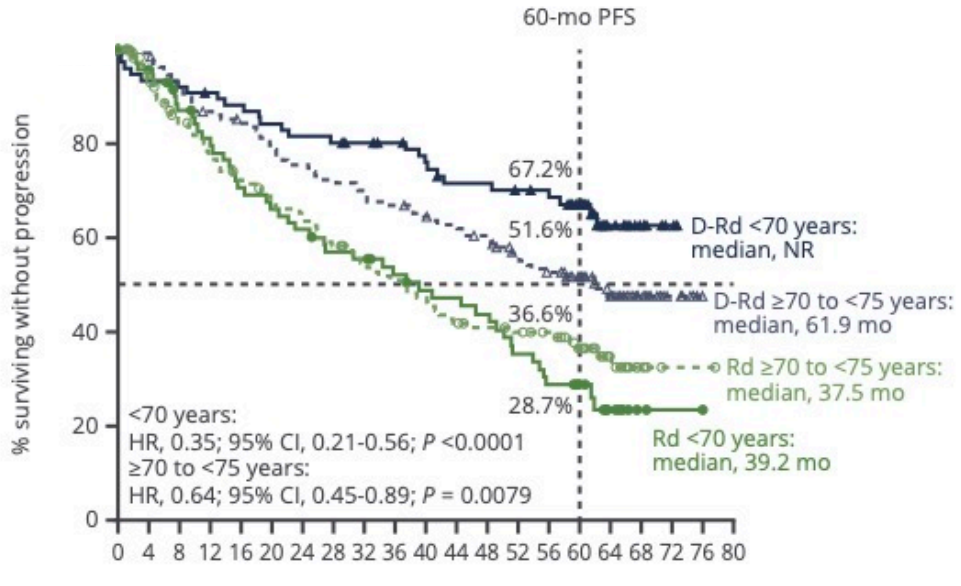
MAIA Age Subgroups: PFS

Median follow-up of 64.5 months

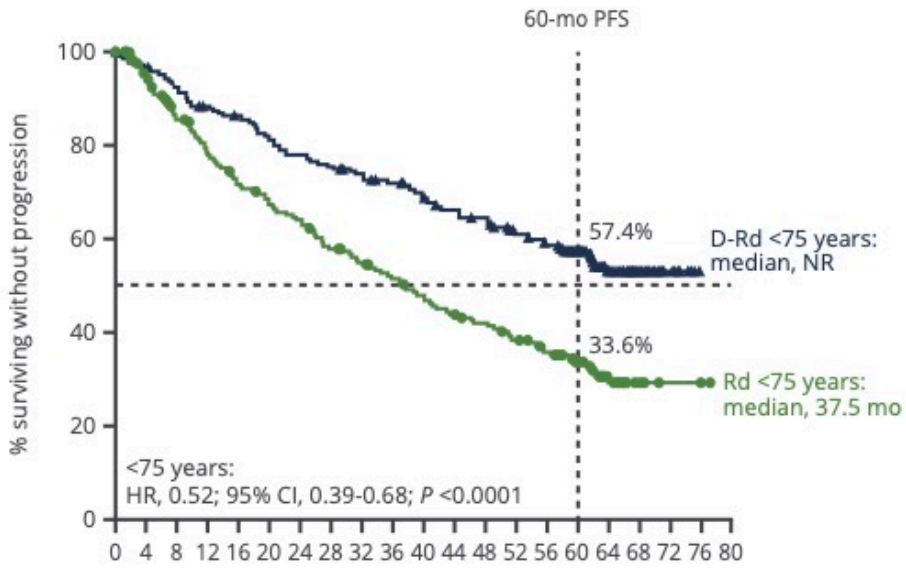
PFS in patients aged <70 years and ≥70 and <75 years



No. at risk

Rd <70 years	77	70	59	53	47	44	41	37	36	32	29	28	26	21	17	13	7	2	1	1	0
D-Rd <70 years	78	72	71	69	67	64	62	61	59	57	54	49	49	47	45	38	19	10	2	0	0
Rd ≥70 to <75 years	131	115	99	89	83	77	74	66	60	56	52	46	43	41	38	28	15	5	1	1	0
D-Rd ≥70 to <75 years	130	127	118	110	106	100	95	91	88	84	81	77	73	64	59	48	33	18	6	0	0

PFS in patients aged <75 years



No. at risk

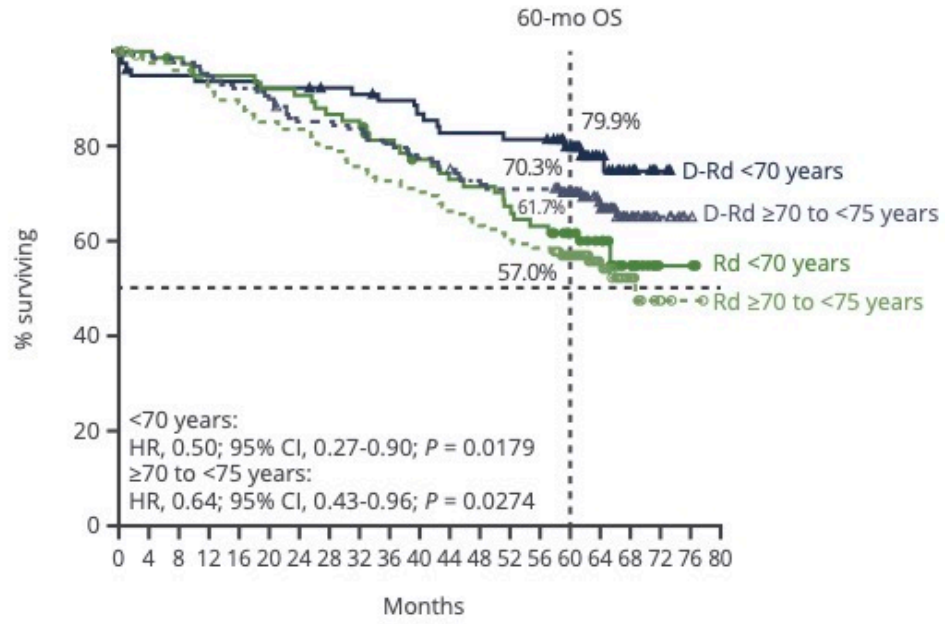
Rd <75 years	208	185	158	142	130	121	115	103	96	88	81	74	69	62	55	41	22	7	2	2	0
D-Rd <75 years	208	199	189	179	173	164	157	152	147	141	135	126	122	111	104	86	52	28	8	0	0

D-Rd, daratumumab, lenalidomide, dexamethasone; NR, not reached; PFS, progression-free survival; Rd, lenalidomide, dexamethasone.

MAIA Age Subgroups: OS

Median follow-up of 64.5 months

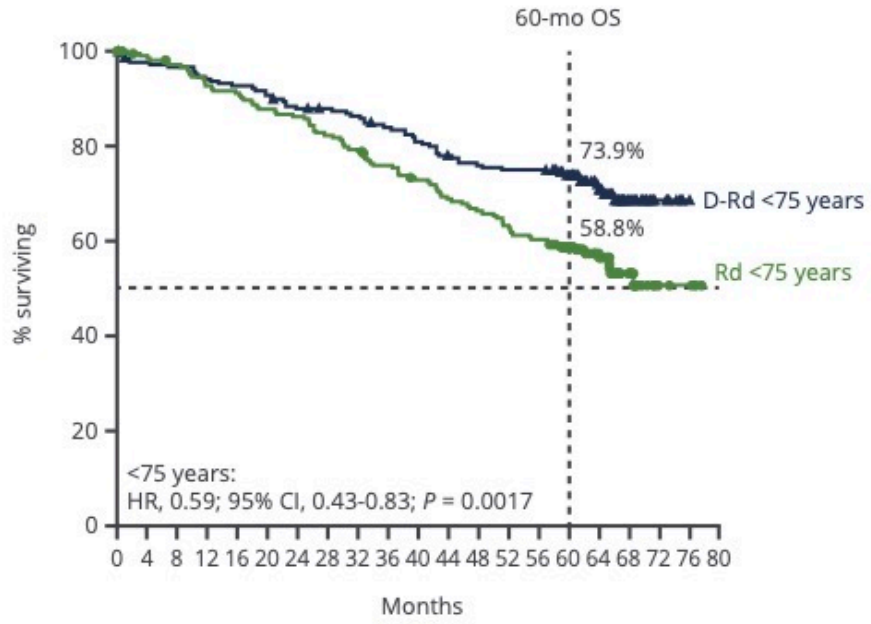
OS in patients aged <70 years and ≥70 and <75 years



No. at risk																				
Rd <70 years	77	76	74	71	71	69	68	65	64	59	55	52	51	48	45	39	29	12	2	2	0
D-Rd <70 years	78	73	73	72	72	71	71	69	68	66	64	61	61	60	60	52	25	14	2	0	0
Rd ≥70 to <75 years	131	126	123	117	114	109	107	102	97	93	90	85	81	78	75	64	35	15	4	1	0
D-Rd ≥70 to <75 years	130	128	126	122	119	116	109	109	107	103	99	95	91	90	90	77	55	25	8	1	0

D-Rd, daratumumab, lenalidomide, dexamethasone; OS, overall survival; Rd, lenalidomide, dexamethasone.

OS in patients aged <75 years



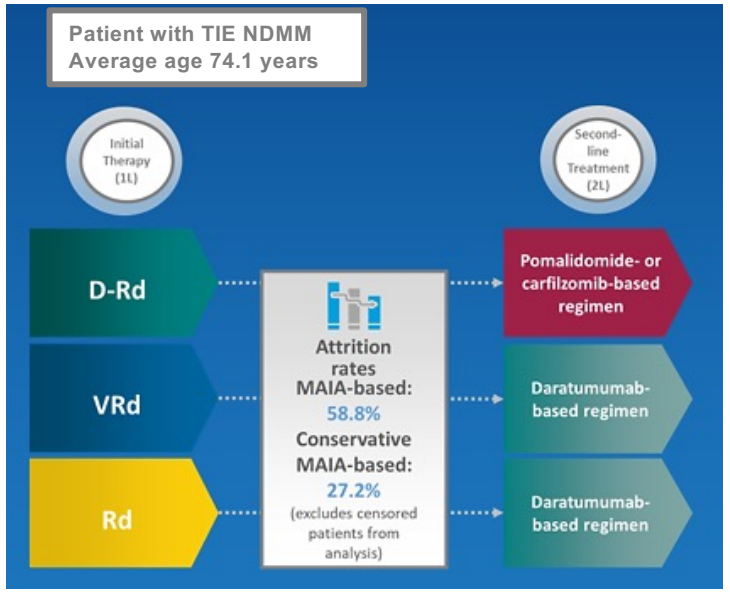
No. at risk																				
Rd <75 years	208	202	197	188	185	178	175	167	161	152	145	137	132	126	120	103	64	27	6	3	0
D-Rd <75 years	208	201	199	194	191	187	180	178	175	169	163	156	152	150	150	129	80	39	10	1	0

Facon T, et al. Presented at: ASH;2022. Abstract 4553.

Treatment Sequencing: Save the Best Until Last?

- 3 potential clinical treatment sequences based on published treatment guidelines to explore OS outcomes

- Time spent in each health state was derived from MAIA, PEGASUS, and the Flatiron health database; 2 attrition rates, both based on MAIA, were incorporated
- Estimated OS rates at 5, 10, and 15 years were highest with D-Rd in 1L
- Incremental OS benefit with D-Rd in 1L was 2.5 years vs VRd in 1L and 3.5 years vs Rd in 1L



Of the 3 treatment sequences, D-Rd in 1L produced estimated OS rates that most closely resembled the general population

Based on available evidence, using D-Rd in 1L is preferable to saving daratumumab for later lines of therapy

1L, first line; 2L, second line; D-Rd, daratumumab, lenalidomide, and dexamethasone; NDMM, newly diagnosed multiple myeloma; OS, overall survival; Rd, lenalidomide and dexamethasone; TIE, transplant-ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

*Average age 74.1 years.
D-Rd, daratumumab, lenalidomide, and dexamethasone; OS, overall survival; Rd, lenalidomide and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone

Fonseca R, et al. *Blood*. 2021;138(Suppl 1):118.

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Multiple Myeloma Includes a Heterogeneous Group of Patients

Moderately fit:
Not regularly active but Routinely walking

Very fit:
active, who exercise regularly

Vulnerable:
Can perform limited activities but they don't need any help

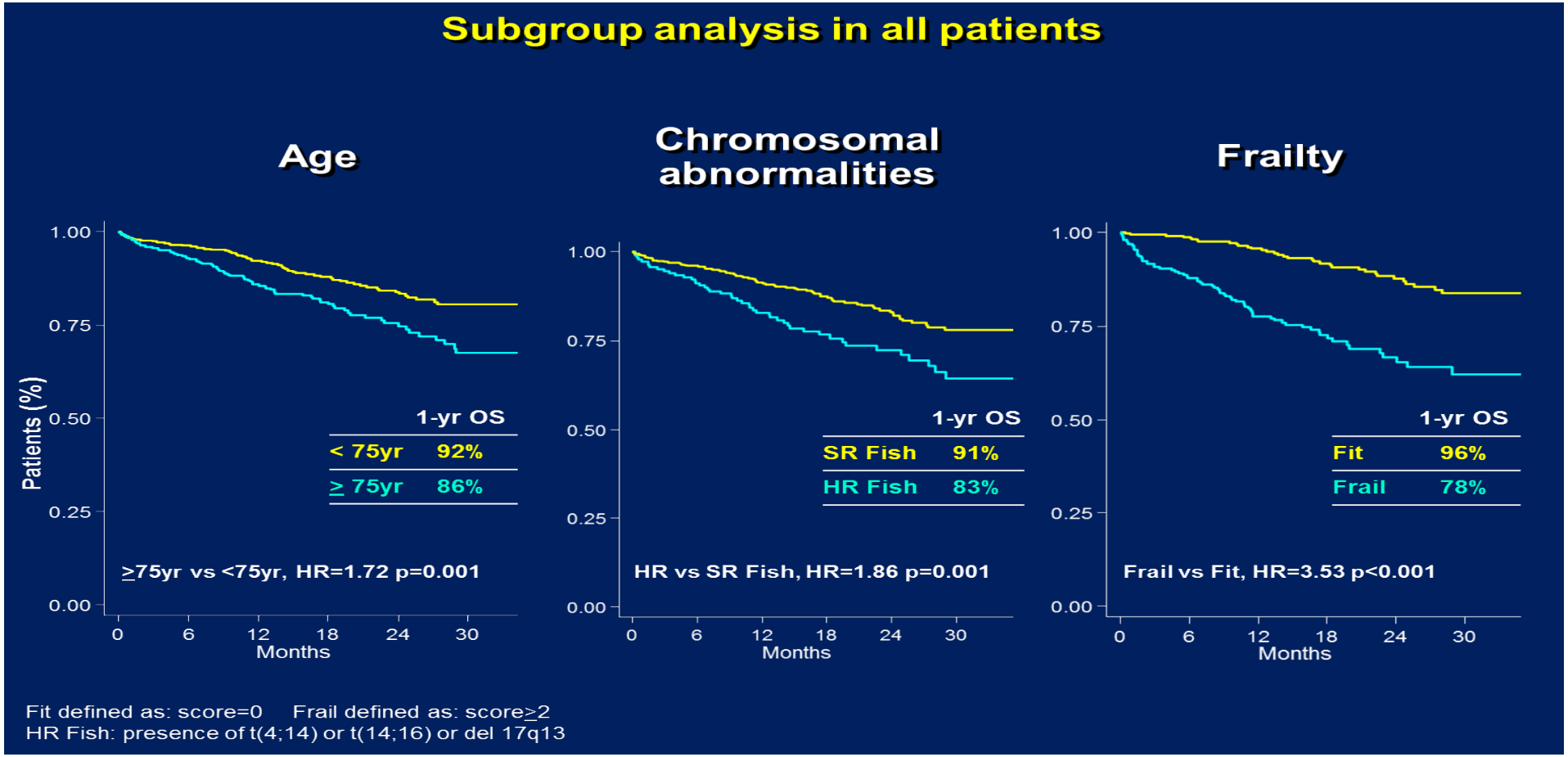
Severely frail:
Dependent on other people

Mildly frail:
Help for household tasks

Moderately frail:
Partial help for their personal care

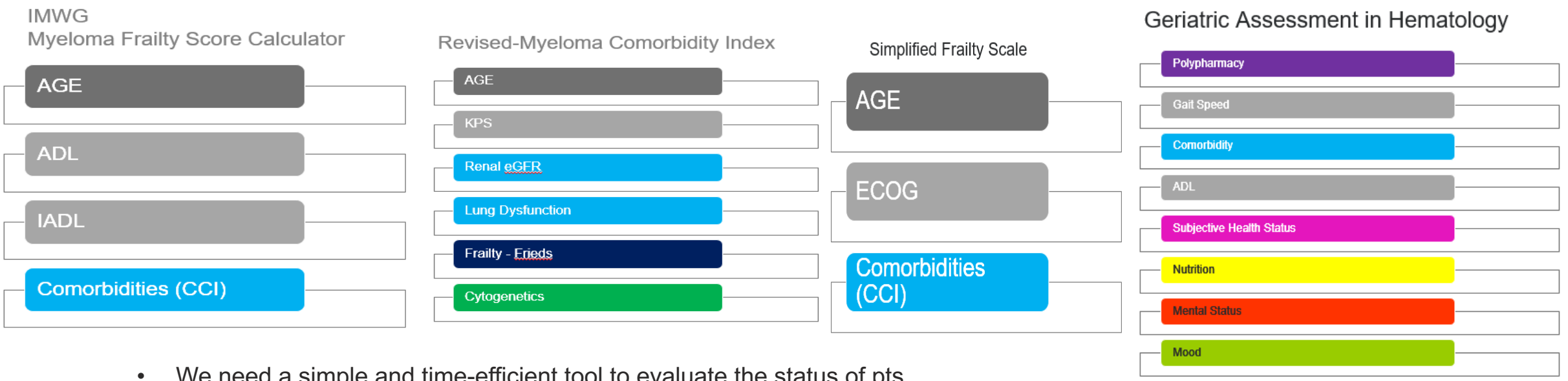
Palumbo A. *Blood*. 2011;118:4519-29.

Factors Predicting Overall Survival in Elderly Patients with MM



Palumbo A. *Blood*. 2011;118:4519-29.

Several Indices for Myeloma "Frailty" Assessment

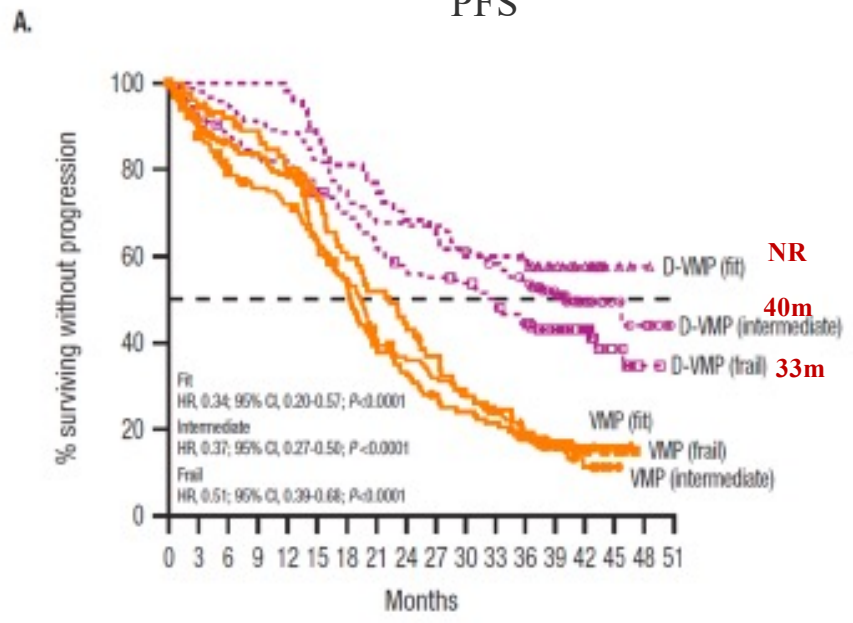


- We need a simple and time-efficient tool to evaluate the status of pts
  - Comorbidities
  - Cognitive condition
  - Physical condition
  - Social condition
- It is not easy and well established the identification of frail patients

Palumbo A, et al. *Blood*. 2015;125(13):2068-74. Engelhardt M, et al. *Haematologica*. 2016;101(9):1110-9. Facon T, et al. *Leukemia*. 2020;34(1):224-233. Bonanad S, et al. *J Geriatr Oncol*. 2015;6(5):353-61.

A Simplified Frailty Scale Has Been Evaluated in the Alcyone Study

PFS

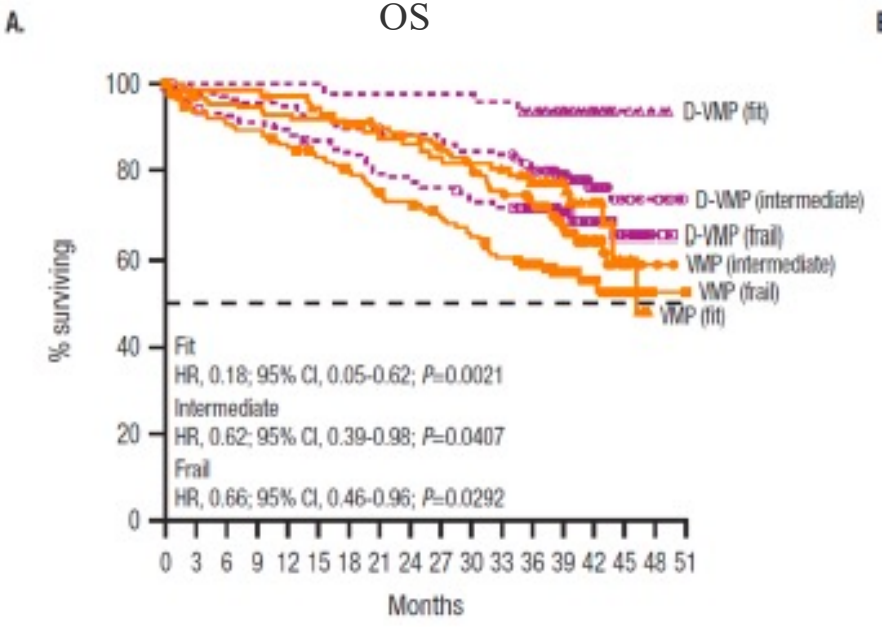


NR

40m

33m

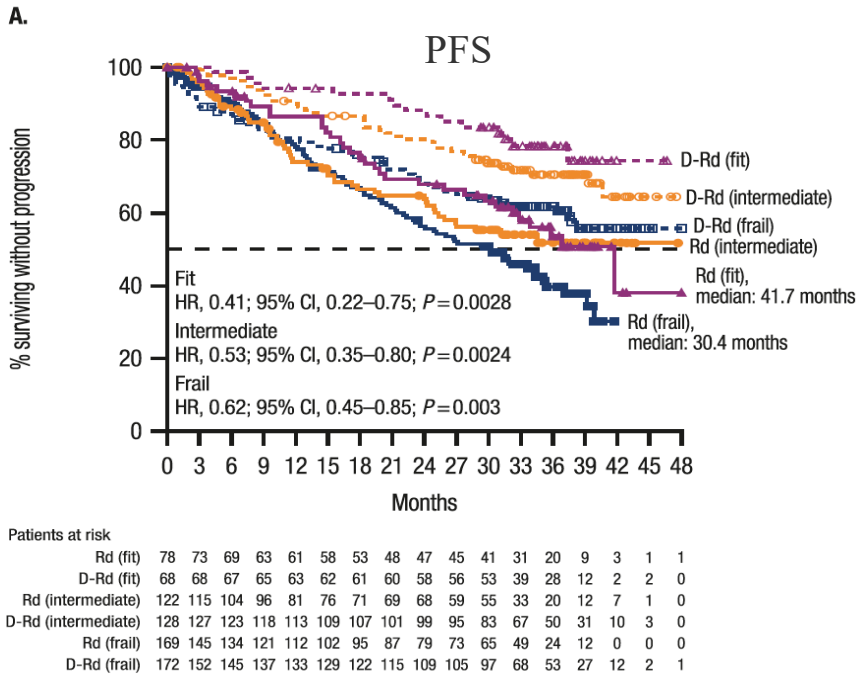
OS

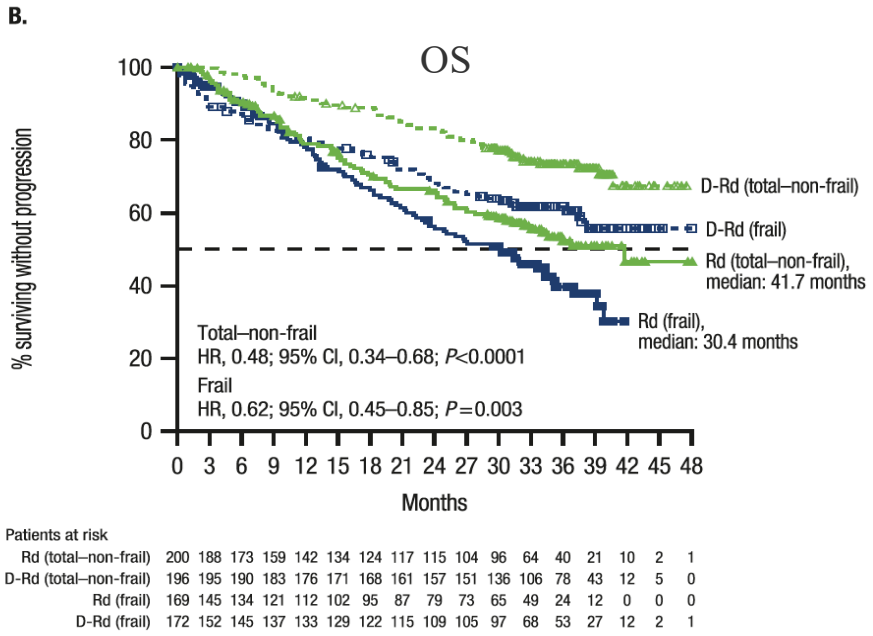


D-VMP is able to overcome the poor prognosis of frailty in terms of PFS

Mateos MV: submitted for publication

A Simplified Frailty Scale Has Been Evaluated in the MAIA Study





D-Rd is able to significantly improve the poor prognosis of frailty in terms of PFS

Facon T, et al. *Leukemia.* 2022;36(4):1066-1077.

Future: Frailty-Adapted Therapy

- Frail patients
- Fit patients

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Ixazomib-Daratumumab and Low-dose Dex in Unfit and Frail NDMM Patients

INCLUSION

- Previously untreated symptomatic MM according to IMWG criteria[1]
- Measurable disease
- Unfit or frail according to IMWG frailty index*
- ANC ≥ 1.0 x 10^9/L and platelets 75 x 10^9/L

EXCLUSION

- Neuropathy grade 1 with pain or ≥ grade 2
- Creatinine clearance < 20 ml/min
- Severe cardiac dysfunction (NYHA III-IV)
- COPD (FEV1 < 50%)
- Active malignancy requiring treatment

INDUCTION

9 cycles of 4 weeks

Ixazomib 4 mg day 1, 8, 15
Daratumumab 16 mg/kg
cycle 1-2 day 1, 8, 15, 22
cycle 3-6 day 1, 15
cycle 7-9 day 1
Dexamethasone
cycle 1-2 20 mg day 1, 8, 15, 22
cycle 3-6 10 mg day 1, 15
cycle 7-9 10 mg day 1

MAINTENANCE

8-week cycles (until progression for a maximum of 2 years)

Ixazomib 4 mg day 1, 8, 15, 29, 36, 43
Daratumumab 16 mg/kg day 1
Dexamethasone 10 mg day 1

Antibiotic and -viral prophylaxis: Cotrimoxazole 480 mg/day, Valaciclovir 500 mg twice daily

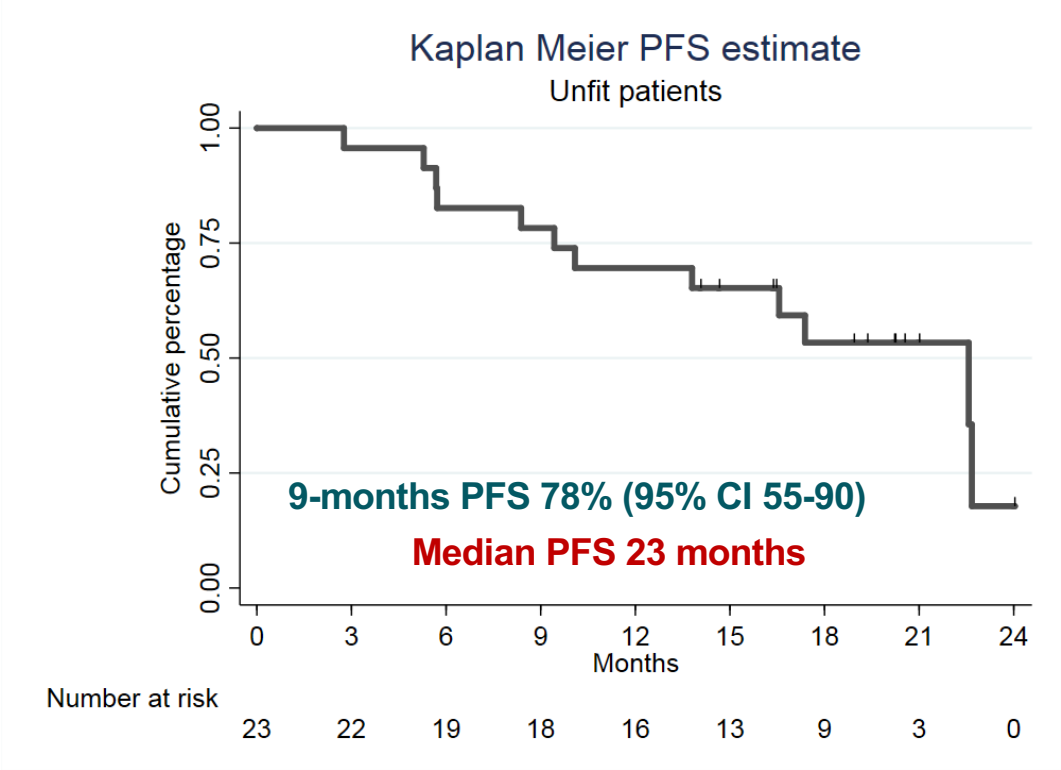
Vaccinations according to local policy

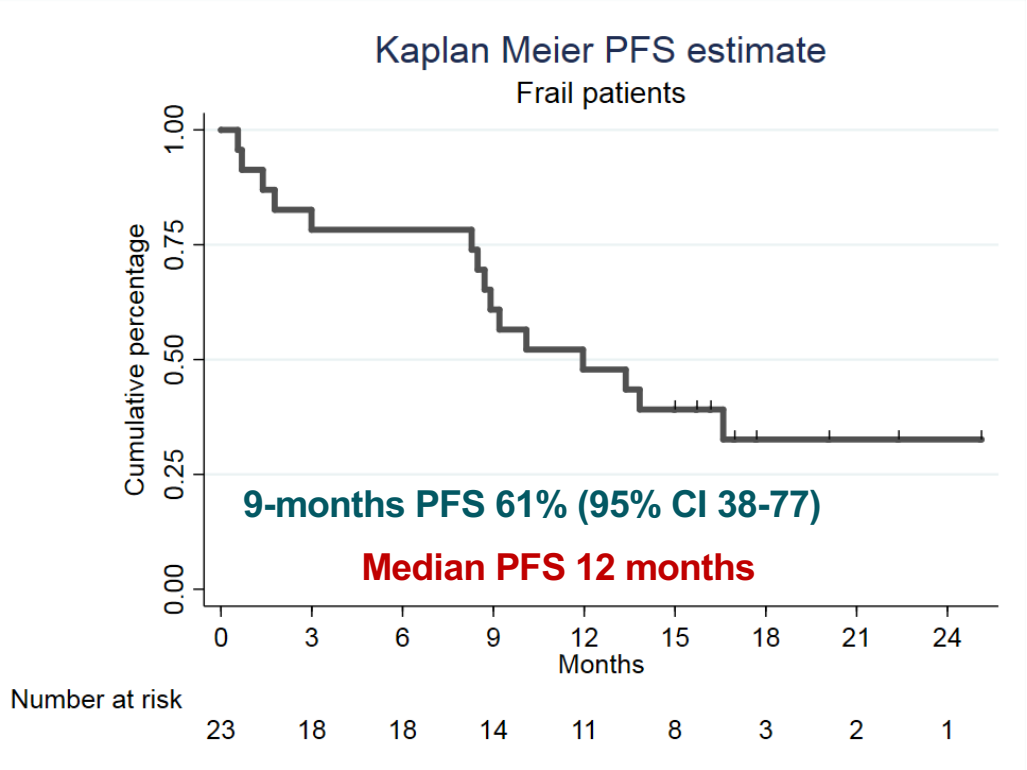
* Age, ADL, IADL and comorbidities

Stege CAM, et al. *J Clin Oncol*. 2021;39(25):2758-2767.

Progression-free Survival

Median follow-up of 18 months

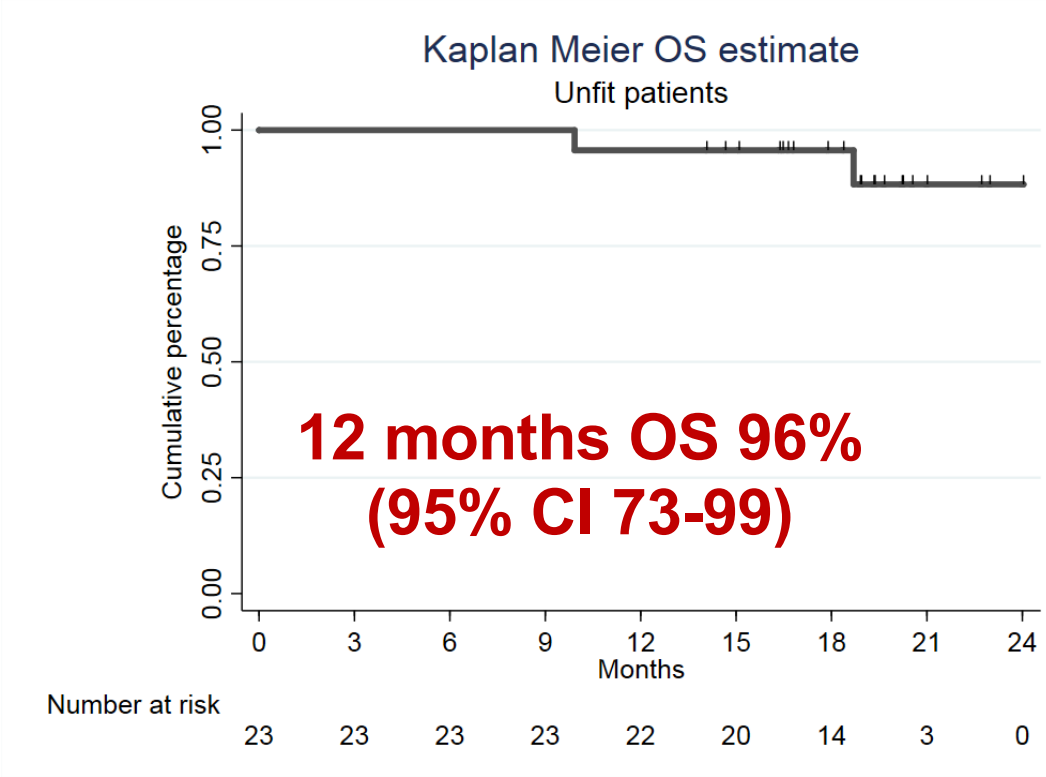


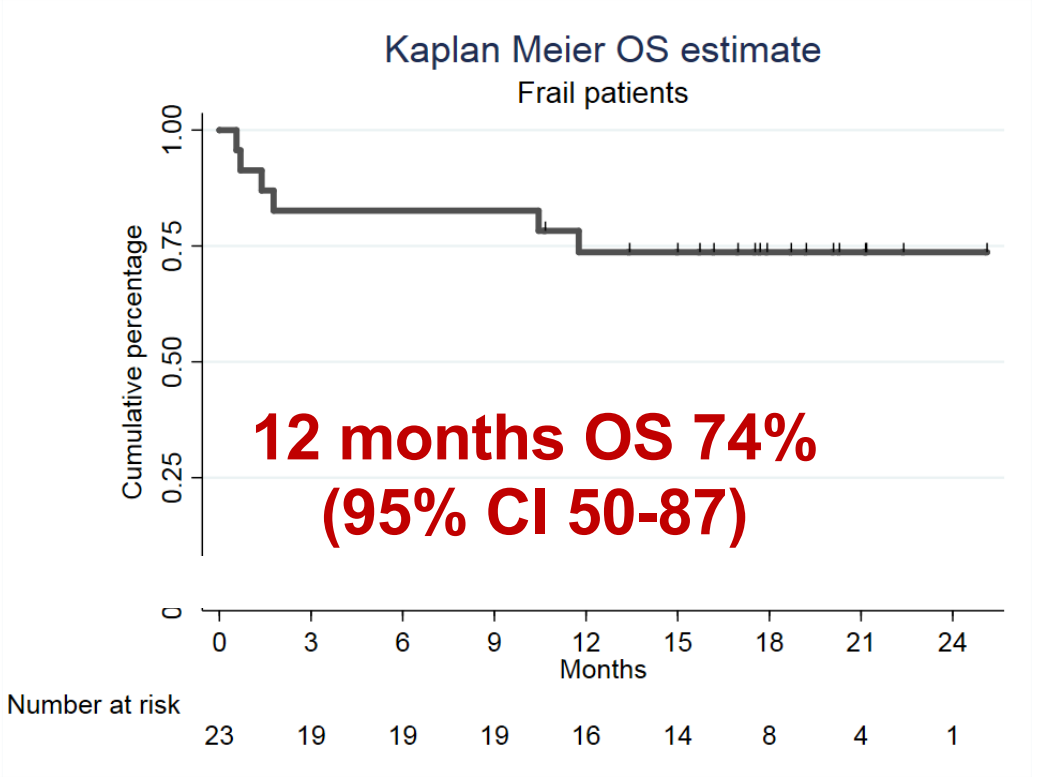


Stege CAM, et al. *J Clin Oncol*. 2021;39(25):2758-2767.

Overall Survival

Median follow-up of 18 months





Stege CAM, et al. *J Clin Oncol*. 2021;39(25):2758-2767.

Safety Profile and Early Death Rate

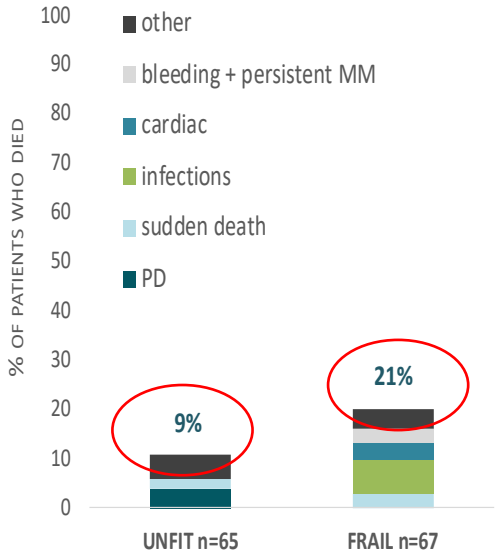
	UNFIT (n=23)		FRAIL (n=23)	
CTCAE grade	III	IV	III	IV
HEMATOLOGICAL n (%)				
Anemia	-	-	-	-
Thrombocytopenia	-	-	4 (17)	1 (4)
Neutropenia	1 (4)	1 (4)	1 (4)	3 (13)

	UNFIT (n=23)		FRAIL (n=23)	
CTCAE grade n (%)	III	IV	III	IV
Gastrointestinal	3 (13)	-	4 (17)	1 (4)
Infections	2 (9)	-	3 (13)	-
Central nervous system	3 (13)	-	2 (9)	-
Cardiac	1 (4)	1 (4)	1 (4)	1 (4)
Peripheral neuropathy	1 (4)	-	1 (4)	-
Secondary primary malignancy	1 (4)	-	1 (4)	-
Skin	-	-	1 (4)	-
Pain	1 (4)	-	-	-
Other	9 (39)	-	4 (17)	4 (17)[1]
VTE any grade[2]	-		1 (4)	

MORTALITY

n=132

MEDIAN FOLLOW UP UNFIT 11.1 MONTHS (3.2-24) AND FRAIL 13.5 MONTHS (0.4-25.1)



Early death rate (≤3 months of registration) - 7%

- **2%** in unfit - 1/65
- **12%** in frail - 8/67
  - 1 before start of therapy
  - 1 decompensated liver cirrhosis
  - 2 sudden death
  - 1 infection
  - 1 bleeding
  - 1 renal failure
  - 1 "pneumonitis"

  } 9%

Ixa-Dara-dex lead to a high response rate and improved quality of life.

However, treatment discontinuation because of toxicity and early mortality, negatively influencing PFS and OS, remains a concern in frail patients. The outcome was heterogeneous across frail subpopulations.

Stege CAM, et al. *J Clin Oncol*. 2021;39(25):2758-2767.

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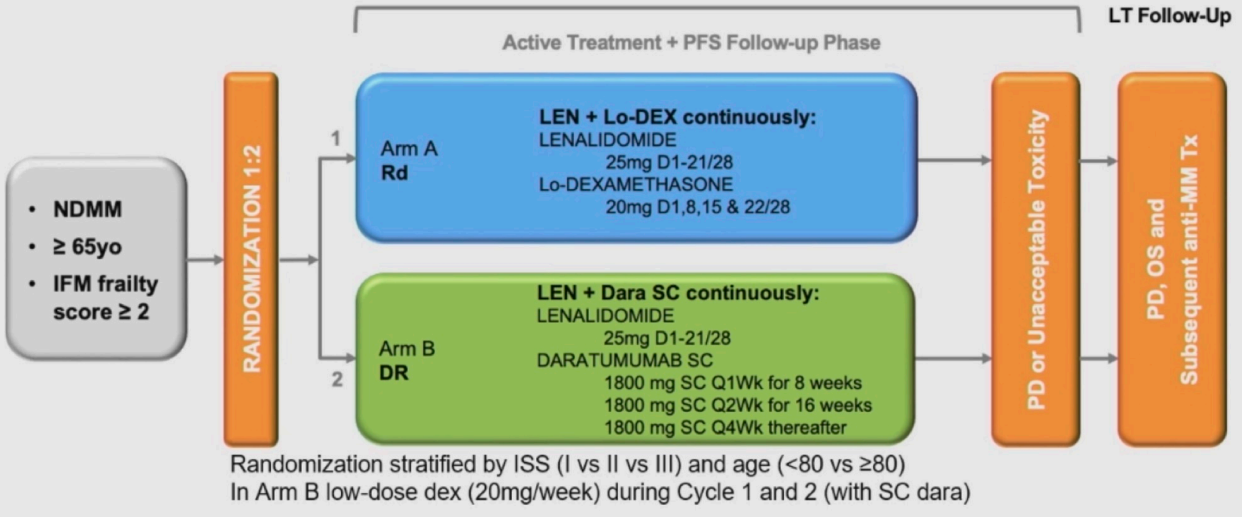
IFM 2017-03: Study Design and Baseline Characteristics for Frail Patients with NDMM

Study design



- Primary endpoint: PFS
- Interim analysis endpoints –12-months-therapy data cut:
  - Overall response rate
  - VGPR or better rate
  - MRD rate
  - Occurrence of grade 3 or higher side effects

Table 1 ECOG proxy of IMWG algorithm of frailty

Category	Score
Age	
≤75 years	0
76–80 years	1
>80 years	2
Charlson Comorbidity Index	
≤1	0
>1	1
ECOG performance status	
0	0
1	1
≥2	2
Sum of scores	
Nonfrail	0–1
Frail	≥2

ECOG Eastern Cooperative Oncology Group, *IMWG* International Myeloma Working Group

Baseline characteristics

Baseline characteristics	DR n=199	Rd n=94
Median age, years (range)	81 (68-92	81 (68-90)
>80 years, n (%)	118 (59)	61 (65)
IFM frailty score, n (%)		
≤1	0	0
2	57 (29)	35 (37)
3	81 (41)	26 (28)
4	44 (22)	24 (26)
5	17 (9)	9 (10)
ISS disease stage, n (%)		
I	33 (17)	18 (19)
II	102 (51)	49 (53)
III	64 (32)	26 (28)
High-risk cytogenetics, n (%) Includes del17p, t(4;14), t(4;16),	31 (17)	17 (22)

Dara, daratumumab; DR, daratumumab, lenalidomide; IFM, Intergroupe Francophone du Myélome; ISS, International Staging System; LEN, lenalidomide; MRD, minimal residual disease; NDMM, newly-diagnosed multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Rd, lenalidomide, dexamethasone; SC, subcutaneous; Q1/2/4Wk, every 1/2/4 week(s); Tx, treatment; VGPR, very good partial response.

Manier S, et al. Presented at: ASH;2022. Abstract 569.

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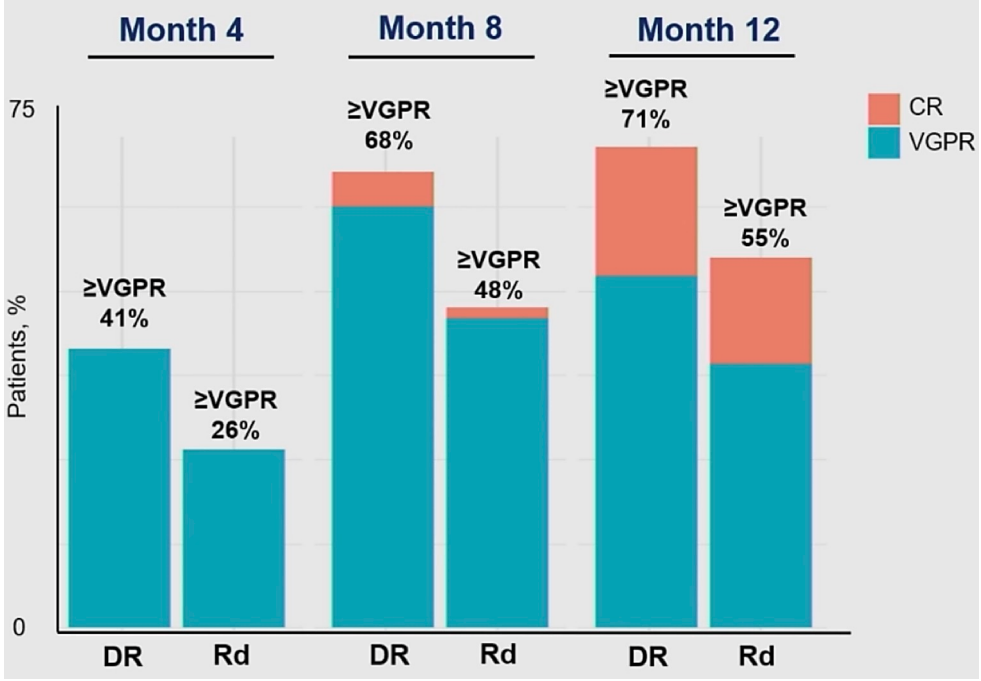
IFM 2017-03: VGPR

Rates of VGPR or better over time



Subgroup analysis of VGPR or better

Subgroup	DR	Rd	OR (95%CI)	pval
Age (years)				**0.66**
≤ 80	56/92 (61%)	16/41 (39%)	0.41 (0.19; 0.87)	
> 80	62/107 (58%)	22/53 (42%)	0.52 (0.26; 1.00)	
Sex				**0.96**
Female	63/101 (62%)	21/48 (44%)	0.47 (0.23; 0.94)	
Male	55/98 (56%)	17/46 (37%)	0.46 (0.23; 0.92)	
ECOG				**0.46**
0-1	64/112 (57%)	24/57 (42%)	0.55 (0.25; 1.21)	
≥ 2	54/87 (62%)	14/37 (38%)	0.37 (0.17; 0.82)	
Charlson Index				**0.85**
0	72/116 (62%)	24/57 (42%)	0.44 (0.23; 0.85)	
1	46/83 (55%)	14/37 (38%)	0.49 (0.22; 1.08)	
IFM frailty score				**0.87**
2	38/57 (67%)	15/35 (43%)	0.38 (0.16; 0.89)	
3	46/81 (57%)	10/26 (38%)	0.48 (0.19; 1.17)	
4/5	34/61 (56%)	13/33 (39%)	0.52 (0.22; 1.22)	
IMWG frailty score				**0.35**
Fit	3/5 (60%)	1/2 (50%)	0.67 (0.02;18.06)	
Intermediate	27/42 (64%)	5/18 (28%)	0.21 (0.06; 0.72)	
Frail	88/152 (58%)	32/74 (43%)	0.55 (0.32; 0.97)	
ISS stage				**0.32**
I	17/33 (52%)	8/18 (44%)	0.75 (0.24; 2.39)	
II	63/102 (62%)	17/49 (35%)	0.33 (0.16; 0.67)	
III	38/64 (59%)	13/26 (50%)	0.68 (0.27; 1.71)	
Cytogenetics profile				**0.29**
Standard risk	90/148 (61%)	24/60 (40%)	0.43 (0.23; 0.79)	
High risk	19/31 (61%)	4/17 (24%)	0.19 (0.05; 0.74)	
Creatinine clearance (mL/min)				**0.68**
< 60	72/120 (60%)	23/53 (43%)	0.51 (0.27; 0.98)	
≥ 60	46/79 (58%)	15/41 (37%)	0.41 (0.19; 0.90)	
All	**118/199 (59%)**	**38/94 (40%)**	**0.47 (0.28;0.77)**	

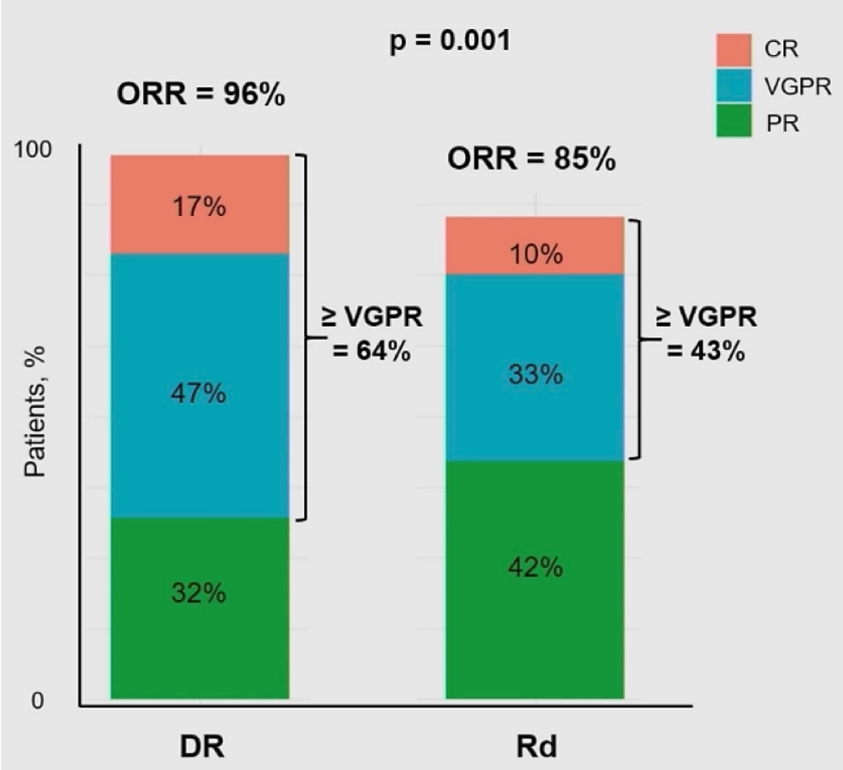
DR improved rates of VGPR or better across all subgroups

CR, complete response; DR, daratumumab, lenalidomide; ECOG, Eastern Cooperative Oncology Group; IFM, Intergroupe Francophone du Myélome; IMWG, International Myeloma Working Group; ISS, International Staging System; Rd, lenalidomide, dexamethasone; VGPR, very good partial response.

Manier S, et al. Presented at: ASH;2022. Abstract 569.

IFM 2017-03: Overall Response, MRD and Safety

Overall response rates



Most common grade ≥3 AEs

	DR group (n=199) Grade ≥ 3	Rd group (n=94) Grade ≥ 3	P value
All grade ≥ 3 AEs, % (n)	82% (164)	68% (64)	0.010
SAE, % (n)	55% (109)	63% (59)	0.21
Hematologic, % (n)	55% (109)	26% (24)	<0.0001
anemia	11% (21)	2% (2)	0.010
neutropenia	46% (91)	18% (17)	<0.0001
thrombocytopenia	9% (18)	3% (3)	0.089
Infection, % (n)	13% (26)	18% (17)	0.29
non-COVID infections	9% (17)	14% (13)	0.21
pneumonia	3% (5)	7% (7)	0.060
COVID	5% (9)	4% (4)	1

	DR group (n=199)	Rd group (n=94)	P value
Treatment discontinuation for AE, % (n)	14% (27)	16% (15)	0.65

- MRD (NGS, 10^{-5}) was assessed in patients with ≥VGPR at 12 months: DR 10% vs Rd 3%, P=0.012

CR, complete response; DR, daratumumab, lenalidomide; IFM, Intergroupe Francophone du Myélome;
ORR, overall response rate; PR, partial response; Rd, lenalidomide, dexamethasone; SAE, serious adverse events; VGPR, very good partial response.

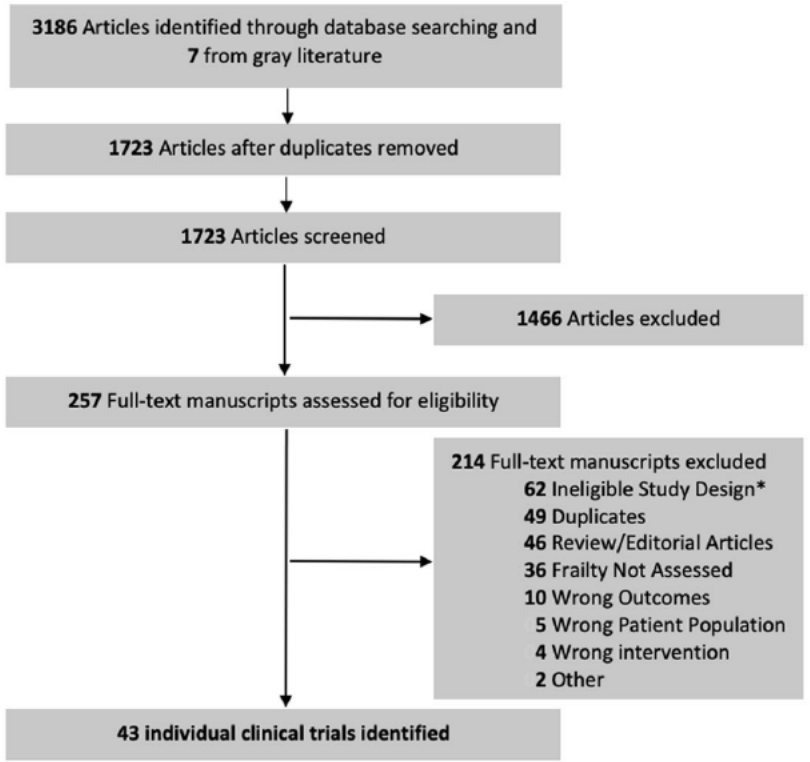
Manier S, et al. Presented at: ASH;2022. Abstract 569.

ARTICLE OPEN

Check for updates

The prevalence and outcomes of frail older adults in clinical trials in multiple myeloma: A systematic review

Hira Mian[1✉], Arleigh McCurdy[2], Smith Giri[3], Shakira Grant[4], Bram Rochwerg[5,6], Erica Winks[1], Ashley E. Rosko[7], Monika Engelhardt[8], Charlotte Pawlyn[9,10], Gordon Cook[11], Graham Jackson[12], Sara Bringhen[13], Thierry Facon[14,15], Alessandra Larocca[16], Sonja Zweegman[17] and Tanya M. Wildes[18]



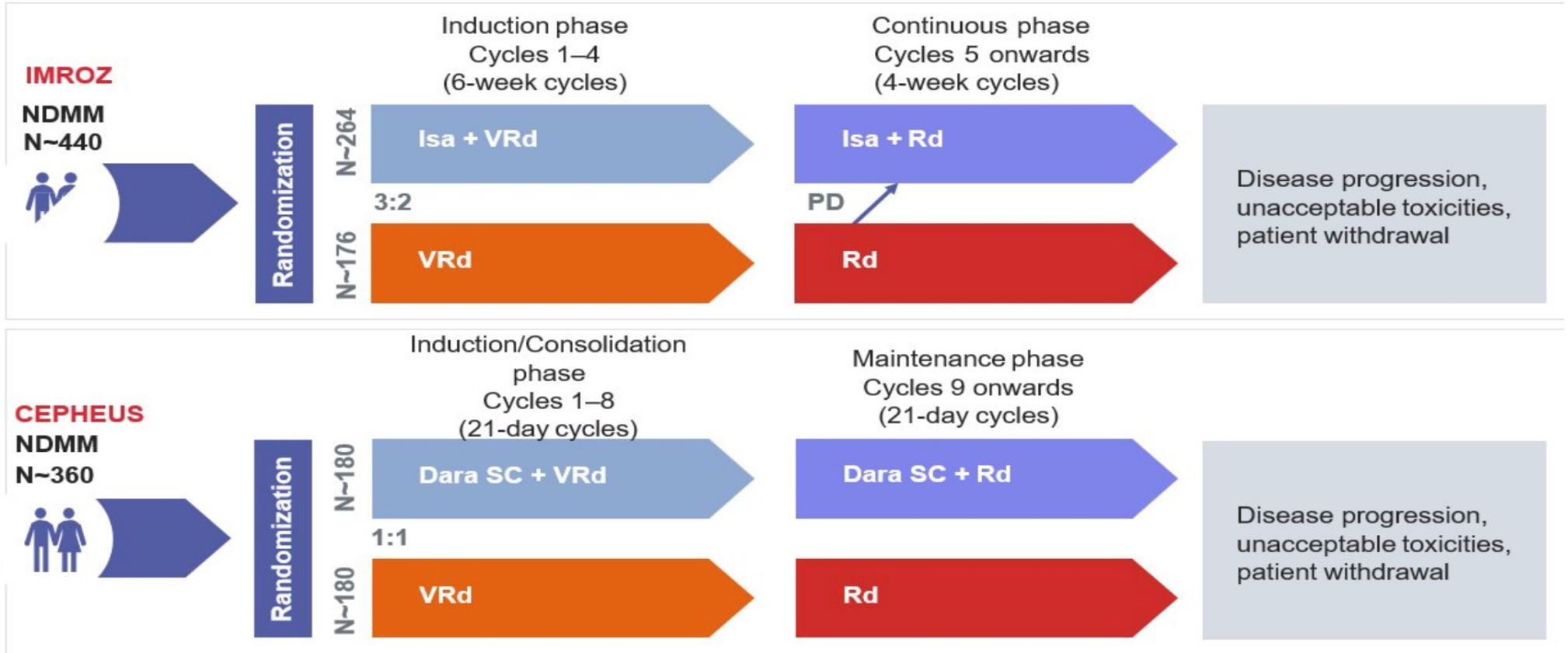
- In conclusion, this systematic review summarizes how frailty is incorporated into therapeutic MM trials and highlights potential areas for future research. Although frailty assessments are being increasingly incorporated into trial designs, there remains wide heterogeneity in both the definition, categorization and cut-off for frailty among the different trials which may limit our ability to evaluate any associated outcomes.

Future strategies aimed at standardizing frailty assessments, along with incorporation of frailty measures in the primary clinical trial design will be critical in operationalizing frailty and using fitness-based approaches to tailor the care of older frail older adults with MM.

Mian H, et al. *Blood Cancer J.* 2023;13(1):6.

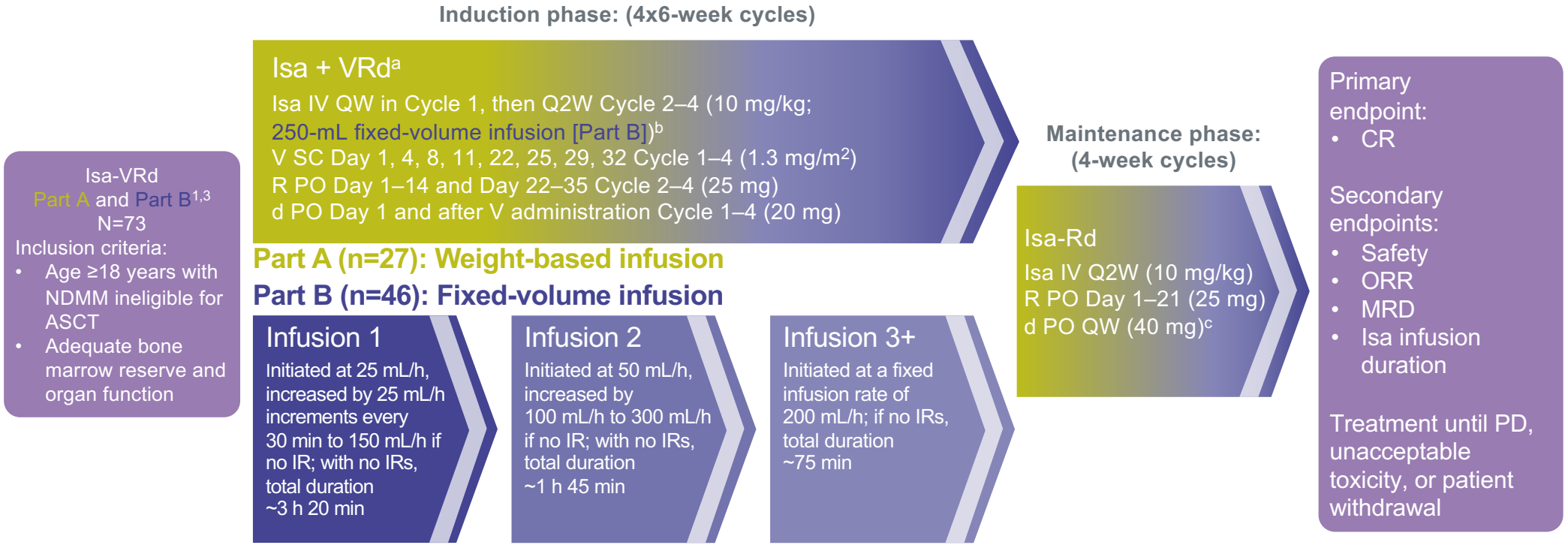
Fit TIE NDMM Patients

Phase III IMROZ & CEPHEUS: Study Designs



Bobin A, et al. Blood. 2022;140(Suppl 1):4423–4425.

TCD13983: Phase I of Isa-VRD in Elderly NDMM



[a]Pre-medications included diphenhydramine 25–50 mg IV (or equivalent), dexamethasone 20 mg IV/PO, ranitidine 50 mg IV (or equivalent), acetaminophen 650–1000 mg PO, montelukast 10 mg PO (or equivalent). The use of montelukast was strongly recommended in Cycle 1, optional from Cycle 2 onward
[b]Isa 10 mg/kg diluted and administered IV from a fixed-volume infusion bag containing 250 mL of 0.9% sodium chloride solution
[c]20 mg/day in patients >75 years old

ASCT, autologous stem cell transplant; d, dexamethasone; h, hour; IR, infusion reaction; Isa, isatuximab; IV, intravenously; min, minute; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PD, progressive disease; PO, orally; QW, once weekly; Q2W, once every two weeks; R, lenalidomide; SC, subcutaneous; V, bortezomib

Ocio E, et al. Presented at: IMW;2021.
NCT02513186. Updated April 28, 2023. Accessed August 22, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT02513186.

Isa-VRd in TIE NDMM Patients: Efficacy

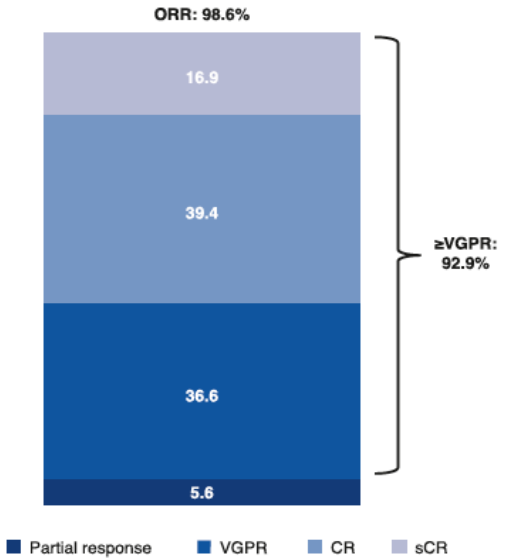
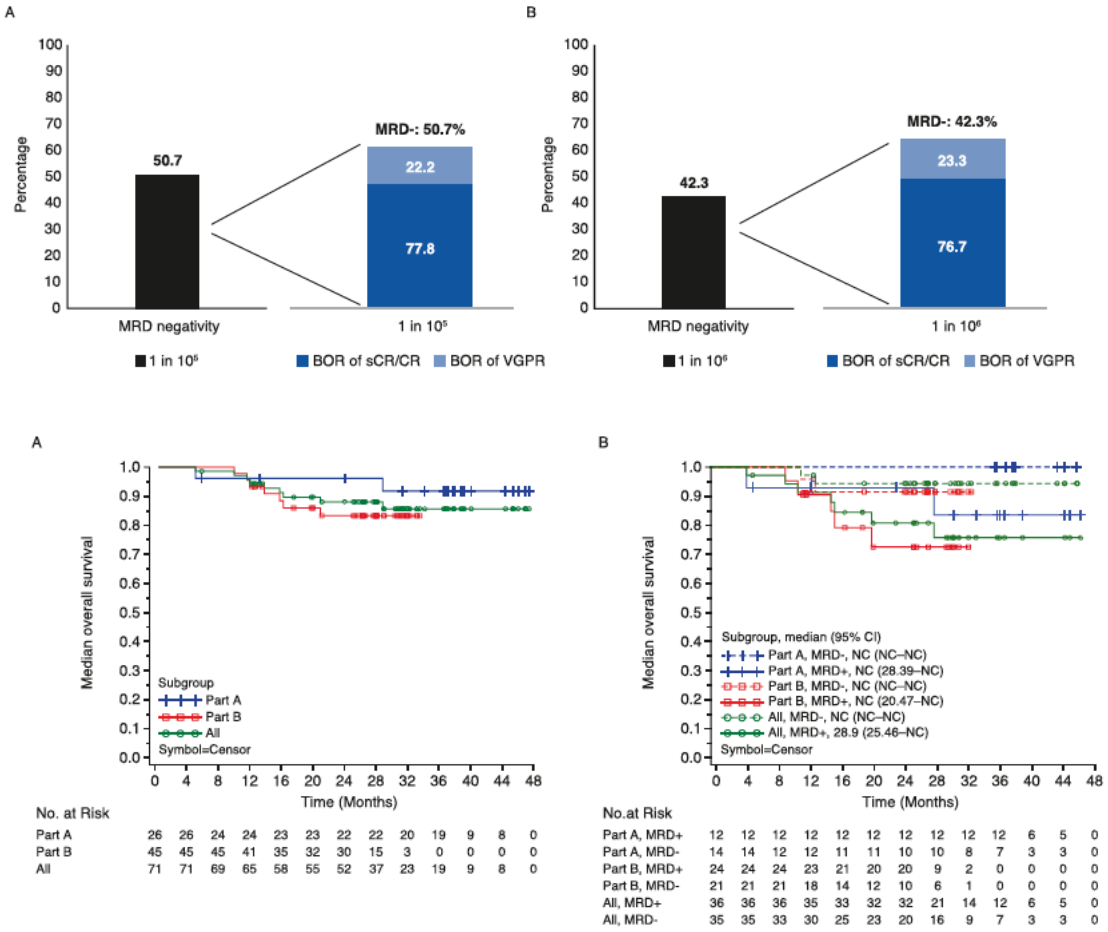


Fig. 2 Best overall response in the efficacy population ($n = 71$)[a]. [a]Data adjusted by incorporating results from 8 (Part A) or 21 (Part B) patients whose samples underwent HYDRASHIFT 2/4 isatuximab IFE testing, an immunofixation test assessing serum M-protein without isatuximab interference. The HYDRASHIFT 2/4 isatuximab IFE assay was launched by Sebia in Europe in February 2021 and approved by FDA in November 2021. CR complete response, IFE immunofixation electrophoresis, sCR stringent complete response, VGPR very good partial response.



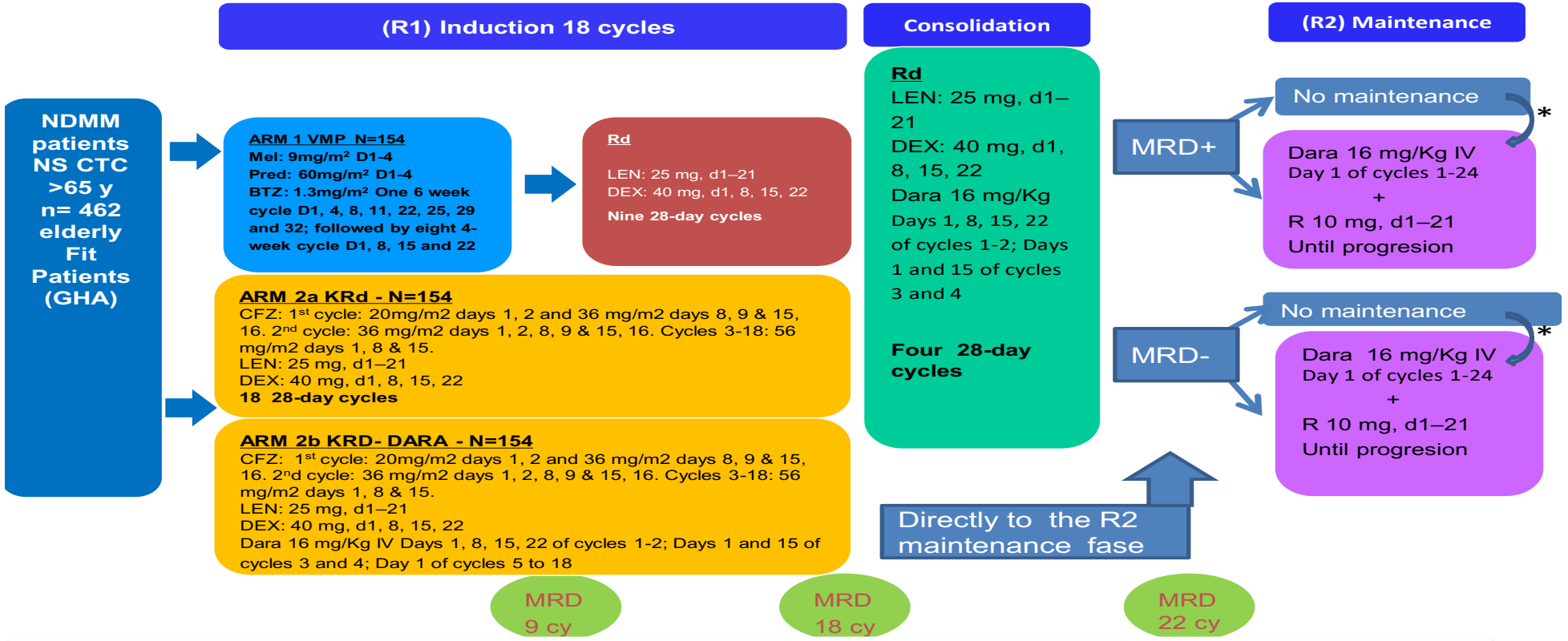
Ocio EM, et al. *Leukemia*. 2023;37(7):1521-1529.

Isa-VRd in TIE NDMM: Safety Profile

n (%)	All-treated population (N=46)	
	All grades	Grade ≥3
Constipation	32 (69.6)	1 (2.2)
Asthenia	31 (67.4)	3 (6.5)
Diarrhea	26 (56.5)	4 (8.7)
Peripheral sensory neuropathy	23 (50.0)	1 (2.2)
Peripheral edema	18 (39.1)	2 (4.3)
Insomnia	13 (28.3)	2 (4.3)
Infusion reaction	13 (28.3)	0
Back pain	12 (26.1)	1 (2.2)
Pain in extremity	12 (26.1)	0
Rash	11 (23.9)	1 (2.2)
Nausea	11 (23.9)	0
Dyspnea	10 (21.7)	1 (2.2)
Decreased appetite	10 (21.7)	0
Hematologic abnormalities		
Anemia	46 (100)	3 (6.5)
Lymphopenia	45 (97.8)	35 (76.1)
Neutropenia	41 (89.1)	19 (41.3)
Leukopenia	45 (97.8)	14 (30.5)
Thrombocytopenia	40 (87.0)	16 (34.7)

Ocio E, et al. Presented at: IMW;2021.
NCT02513186. Updated April 28, 2023. Accessed August 22, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT02513186.

GEM2017FIT for Fit TIE NDMM Patients



Primary endpoint immunophenotypic complete response
Secondary exploratory outcome: PFS

* Patientes in Biological relapse will be rechallenge by Dara + R

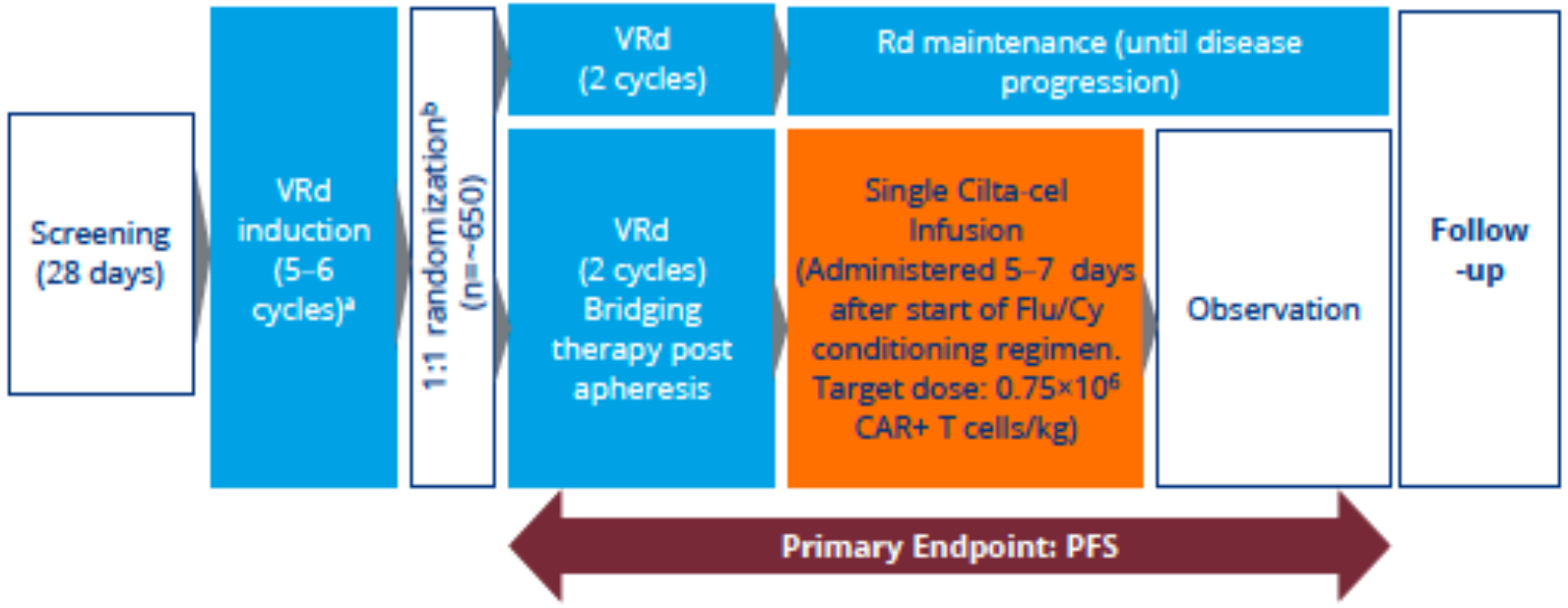
[a]During the first cycle (6 weeks), bortezomib is given on D1, 4, 8, 11, 22, 25, 29, and 32.; GAH: J Geriatr Oncol. 2015 Sep;6(5):353-61; R1: first randomization; R2: second randomization ; IMF immunophenotypic response NGF (next generation flow)

Bonanad S, et al. *J Geriatr Oncol*. 2015;6(5):353-61.

BCMA-CAR-Ts in NDMM Patients TIE

Cartitude-5

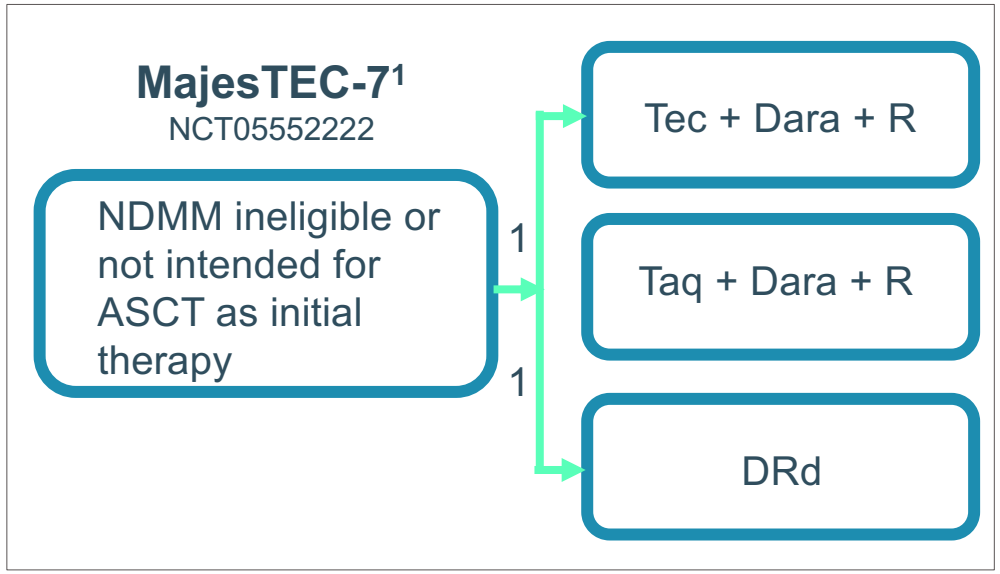
FIGURE 1: CARTITUDE-5 Study Design

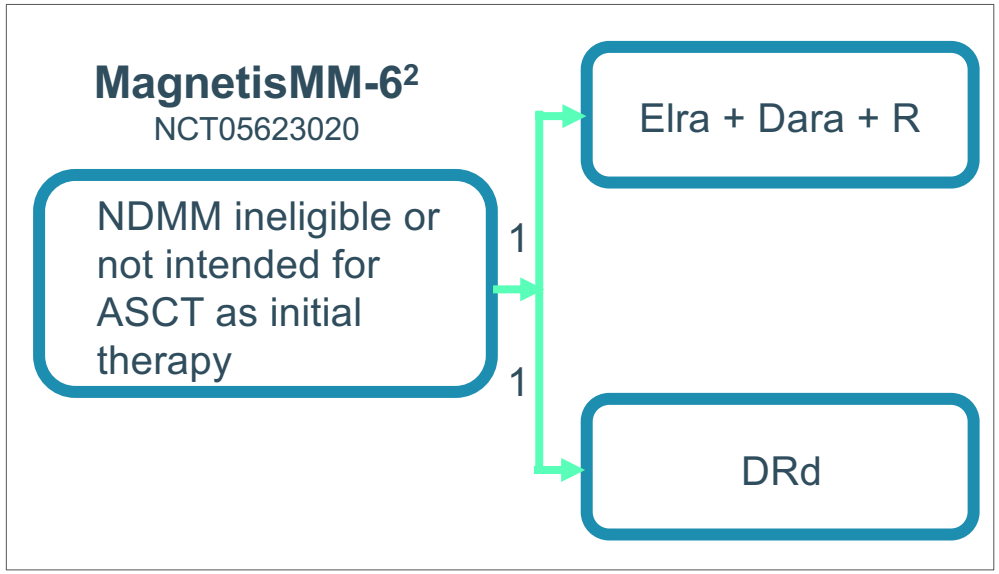


Flu, fludarabine; Cy, cyclophosphamide
[a] 1 cycle VRd allowed prior to screening
[b] At randomization, patients will be stratified by the following factors: R-ISS (I,II,III); age/transplant eligibility (≥70 years or <70 years and ASCT ineligible due to comorbidities or <70 years and ASCT deferred); response to VRd induction (≥VGPR, ≤PR)

NCT04923893. Updated August 16, 2023. Accessed August 22, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT04923893.

BCMA-targeting bispecific antibodies for newly diagnosed **transplant-ineligible** MM patients





ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; CR, complete response; Dara, daratumumab; DRd, daratumumab, lenalidomide, dexamethasone; MM, multiple myeloma; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; R, lenalidomide; Tec, teclistamab.

1. Krishnan AY, et al. Blood. 2022;140:10148–10149; 2. NCT05623020. Available at: https://clinicaltrials.gov/ct2/show/NCT05623020. Accessed April 2023.

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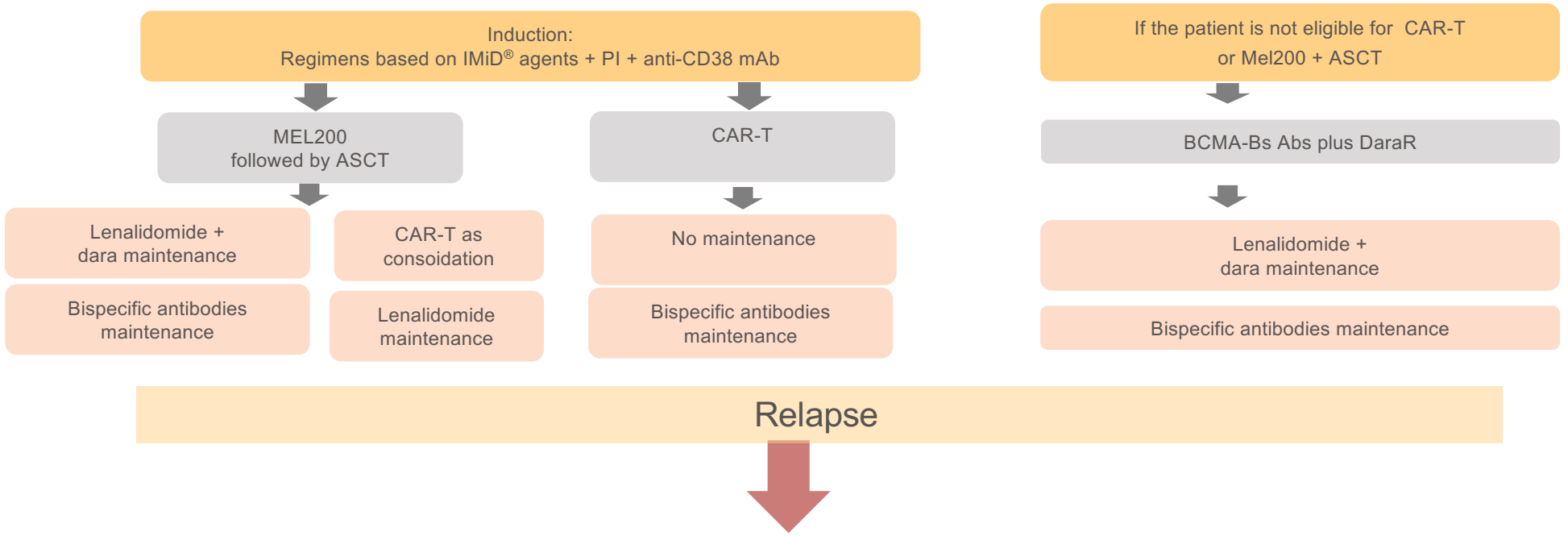
Future Landscape of Therapy for TIE NDMM FIT



- We will change transplant eligibility by CAR-T eligibility
- For the frail population, antiCD38 mABs in combination with IMiDs plus/minus corticosteroids

Summary

- The achievement of undetectable MRD in the TE and TIE is an important prognostic factor and novel approaches are emerging to facilitate its use

Today:

- TIE: DaraRd should be the first choice if the combination is available

In the future:

- The treatment would be frail-adapted for the TIE
- CAR-Ts and Bispecific monoclonal antibodies will be a choice in the first line of therapy and can potentially replace ASCT