Treatment of newly diagnosed MM Non-Transplant Eligible

Professor Thierry Facon

Centre Hospitalier Universitaire de Lille, University of Lille
French Academy of Medicine, Paris, France

Centre Hospitalier Régional Universitaire de Lille

Académie Nationale de Médecine

ifm

Disclosures

- **Thierry Facon**, University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France

– Any compensation received was provided directly to CHU Lille

  - Speakers bureaus: Janssen, Bristol Myers Squibb, Takeda
  - Advisory boards: Janssen, Bristol Myers Squibb, Takeda, Sanofi, Roche, Karyopharm, Oncopeptides, Amgen

Frailty Concept and Assessment

Components of Frailty in Older Patients with Haematological Malignancies

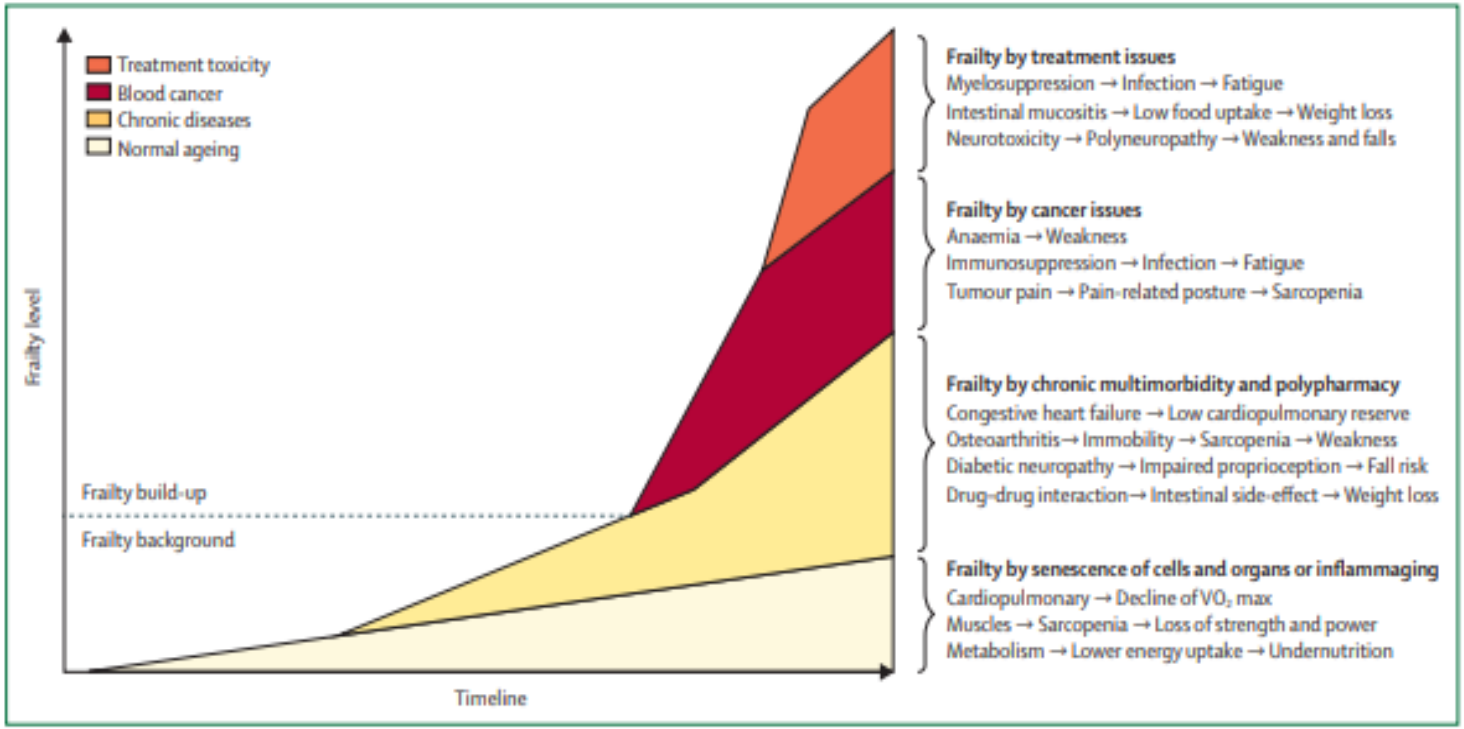
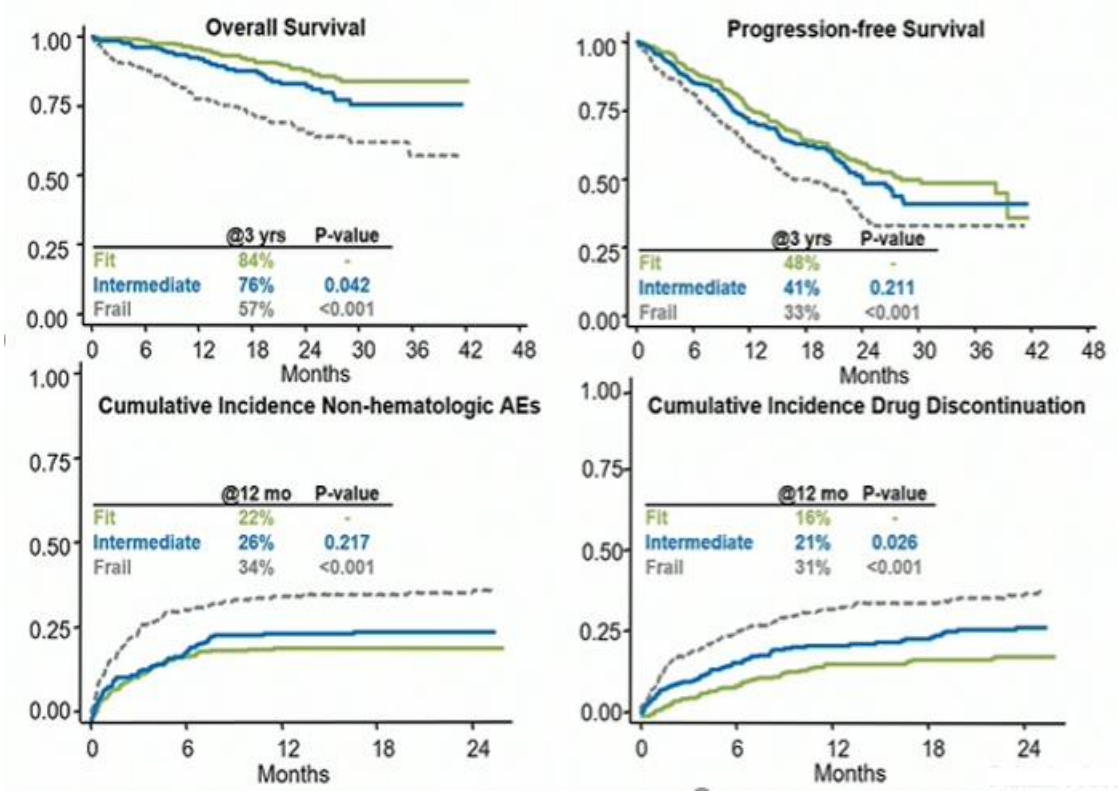
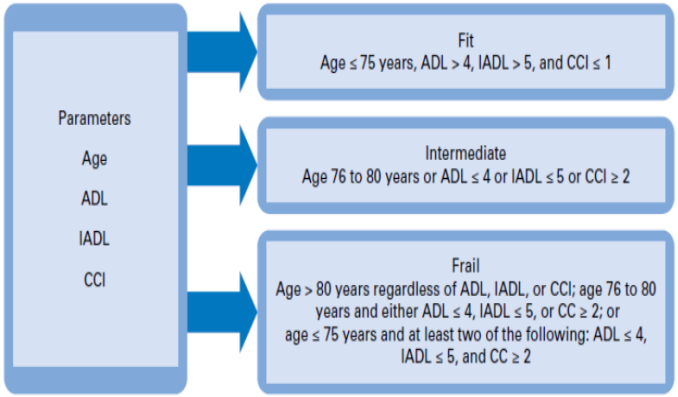


Figure 1: **Components of frailty in older patients with haematological malignancies**
Several examples of pathways to frailty are provided below each of the four scenarios.

Goede V, Neuendorff NR, Schulz RJ, et al. Lancet Healthy Longev 2021;2:e736-45

IMWG Frailty Score





Palumbo A et al. Blood. 2015; 25:2068-2074.
Larocca A Blood 126(19)2174 - 2185, 2015

Various frailty assessment tools

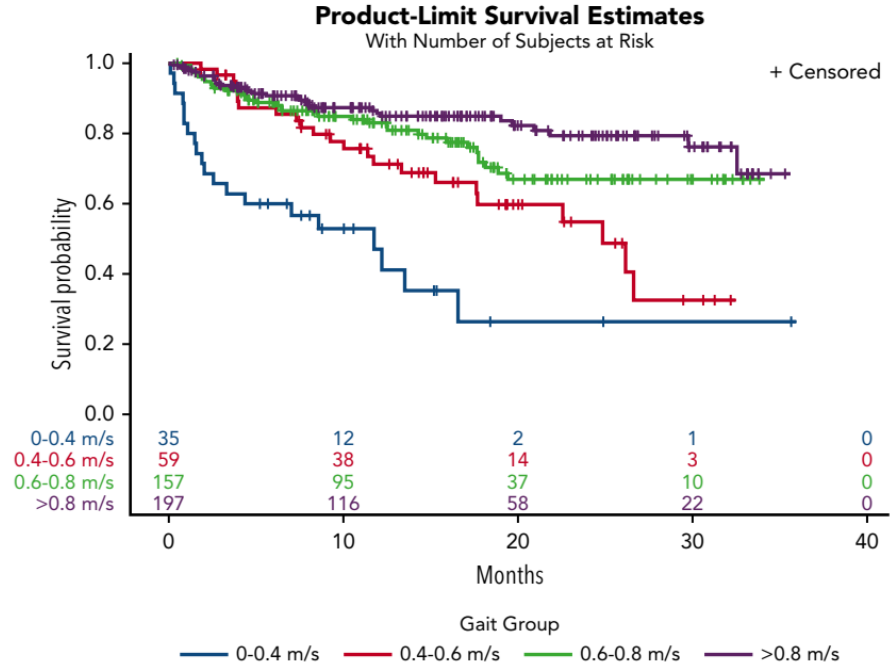
	IMWG frailty score	R-MCI	UKMRA MRP	Mayo risk score	Ancona Vulnerability Score	IFM simplified frailty scale
Biological / Clinical components	Age CCI	eGFR PFTs Frailty Age Cytogenetics	Age R-ISS CRP	Age NT-proBNP	CCI	Age CCI
Functionality tests	ADL IADL	PS (Karnofski)	PS (WHO)	PS (WHO)	PS (WHO)	ECOG
Population	Clinical trials	Clinical trials, real world	Clinical trials, real world	Real world	Real world	Clinical trials

ADL, Activities of Daily Living; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; IADL, Independent Activities of Daily Living; IMWG, International Myeloma Working Group; MM, multiple myeloma; NT-proBNP, N-terminal pro-brain natriuretic peptide; PFT; pulmonary function test; PS, performance status; R-ISS, Revised International Staging System; R-MCI, Revised Myeloma Comorbidity Index; UKMRA MRP, UK Myeloma Research Alliance Myeloma Risk Profile; WHO, World Health Organization

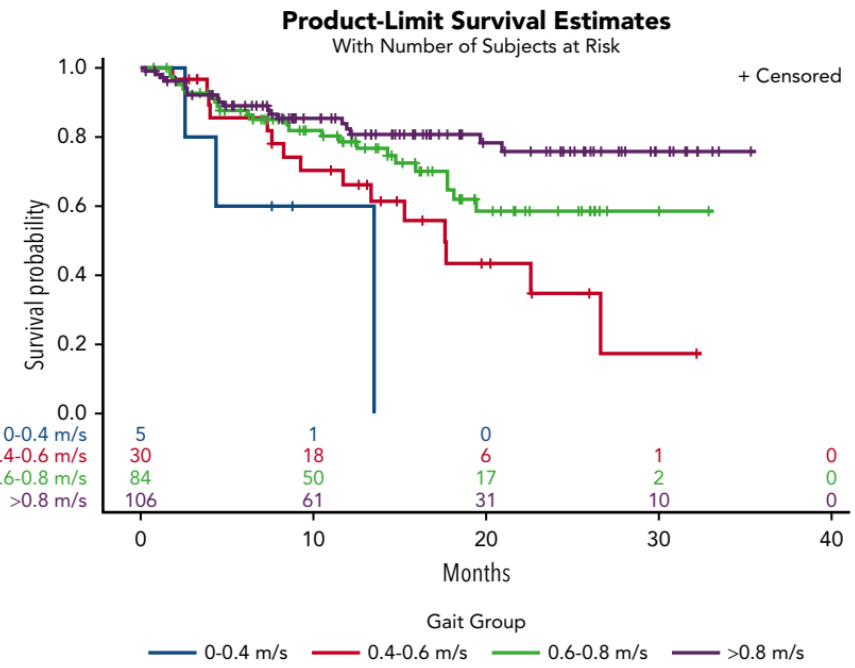
Cook G, et al. Leukemia 2020; 34:2285–94

Gait speed and survival outcomes in elderly patients with hematological malignancies

Survival by gait speed



Survival by gait speed in patients with ECOG PS 0-1

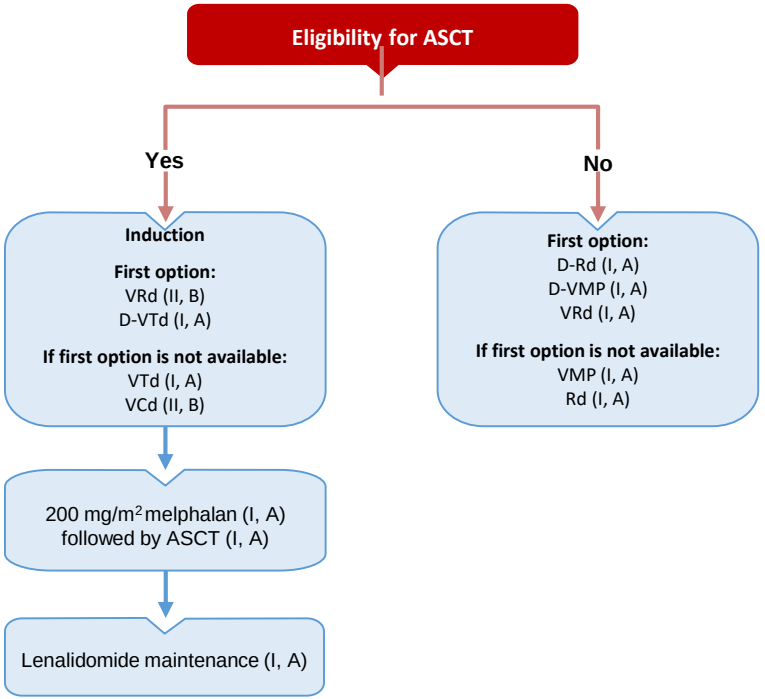


ECOG PS, Eastern Cooperative Oncology Group Performance Status

Liu M et al. Blood 2019; 134(4):374-382

Current Standards of Care

Current EHA-ESMO guidelines for the treatment of MM: frontline management of disease

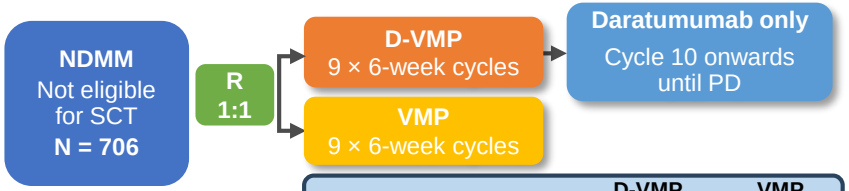


ASCT, autologous stem cell transplantation; D-Rd, daratumumab + lenalidomide + dexamethasone; D-VMP, daratumumab + bortezomib + melphalan + prednisone; D-VRd, daratumumab + bortezomib + lenalidomide + dexamethasone;
D-VTd, daratumumab + bortezomib + thalidomide + dexamethasone; EHA, European Hematology Association; ESMO, European Society for Medical Oncology; Rd, lenalidomide + dexamethasone; VCd, bortezomib + cyclophosphamide + dexamethasone; VMP, bortezomib + melphalan + prednisone; VRd, bortezomib + lenalidomide + dexamethasone; VTd, bortezomib + thalidomide + dexamethasone.

Dimopoulos MA, et al. Ann Oncol. 2021;32:309-22.

Key study designs in non stem-cell transplantation NDMM

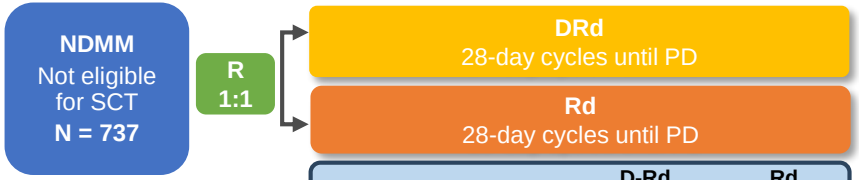
ALCYONE[1]



Primary endpoint: PFS

Characteristic	D-VMP (n = 350)	VMP (n = 356)
Median age (range), years	71 (40–93)	71 (50–91)
Age ≥ 75 years, %	30	30
ECOG PS 0/1/2, %	22/52/26	28/49/24
High-risk cytogenetics, %	17	15

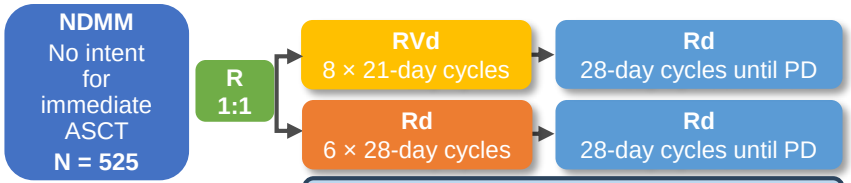
MAIA[2]



Primary endpoint: PFS

Characteristic	D-Rd (n = 368)	Rd (n = 369)
Median age (range), years	73 (50–90)	74 (45–89)
Age ≥ 75 years, %	44	44
ECOG PS 0/1/2, %	35/48/17	33/51/16
High-risk cytogenetics, %	15	14

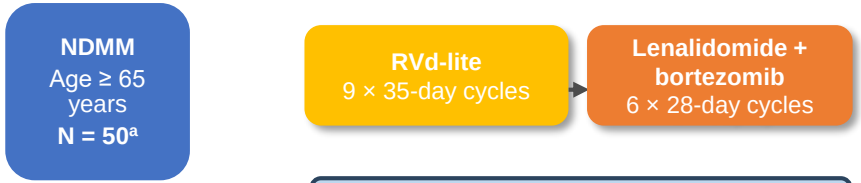
SWOG S0777[3]



Primary endpoint: PFS

Characteristic	RVd (n = 264)	Rd (n = 261)
Median age (range), years	63 (-)	63 (-)
Age ≥ 65 years, %	38	48
ECOG PS > 1, %	12	16
High-risk cytogenetics, %	-	-

RVd-lite[4,a]



Primary endpoint: ORR

Characteristic	ITT (n = 50)
Median age (range), years	73 (65–91)
Age ≥ 75 years, %	-
ECOG PS 0/1/2, %	50/36/14
High-risk cytogenetics, %	12

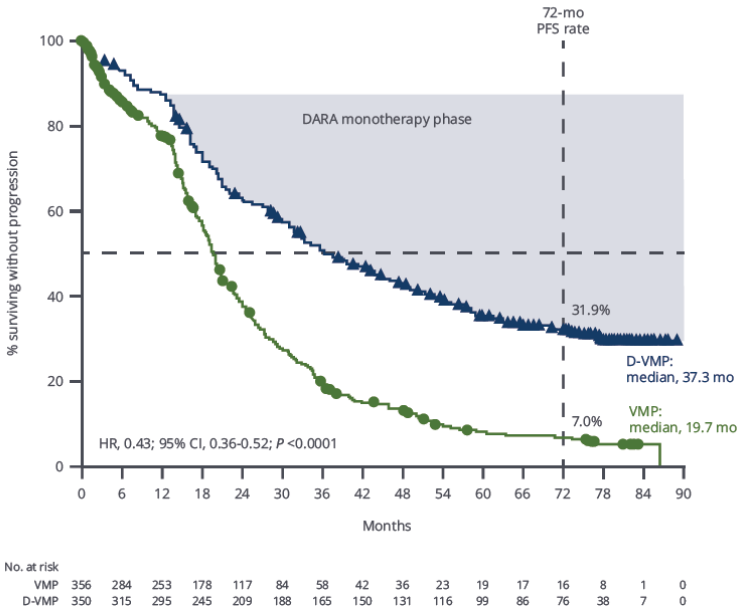
These charts are provided for ease of viewing information from multiple trials.
Direct comparison between trials is not intended and should not be inferred.
[a] RVd lite is phase II, others phase III.
DRd, daratumumab, lenalidomide, low-dose dexamethasone; D-VMP; daratumumab, bortezomib, melphalan, prednisone; R, randomized; SCT, stem-cell transplantation.

1. Mateos MV et al. N Engl J Med 2018;378:518–28. 2. Facon T et al. N Engl J Med 2019;380:2104–15. 3. Durie BGM et al. Lancet 2017;389:519–27. 4. O'Donnell EK, et al. Br J Haematol 2018;182:222–30.

PFS in Daratumumab TNE Studies

ALCYONE

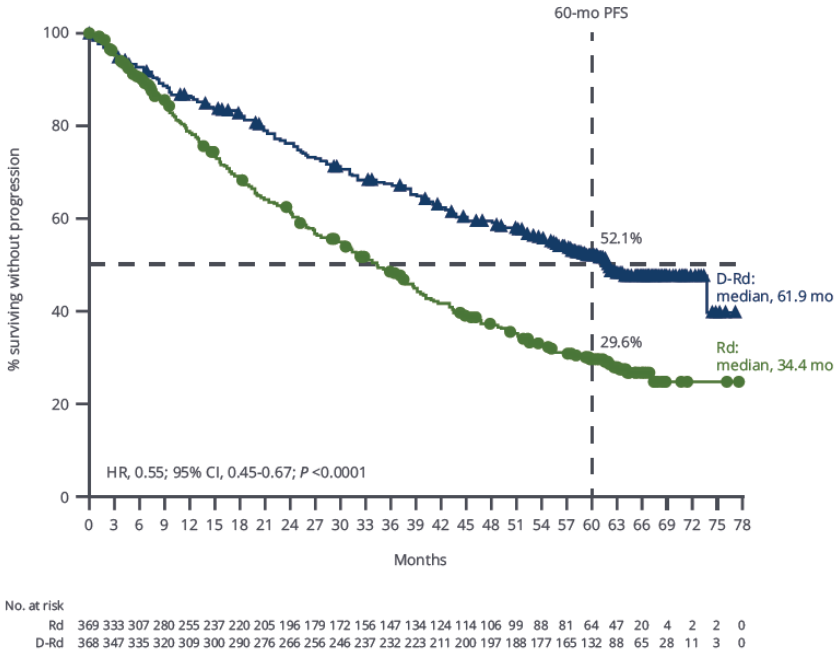
FIGURE 1: PFS based on investigator assessment with D-VMP and VMP in the ITT population



Mateos MV et al ASH 2022.

MAIA

FIGURE 1: PFS with D-Rd and Rd in the ITT population[a]

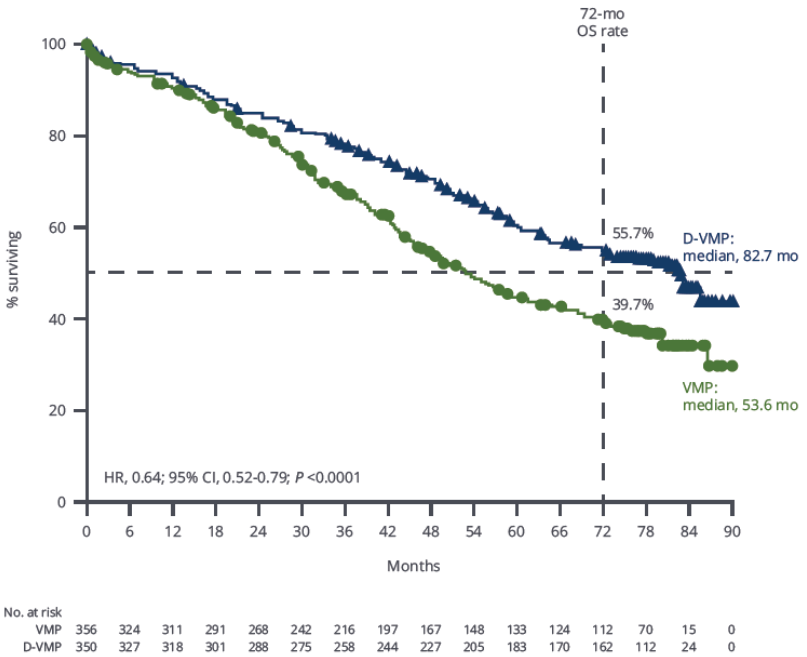


Kumar et al. ASH 2022

OS

ALCYONE

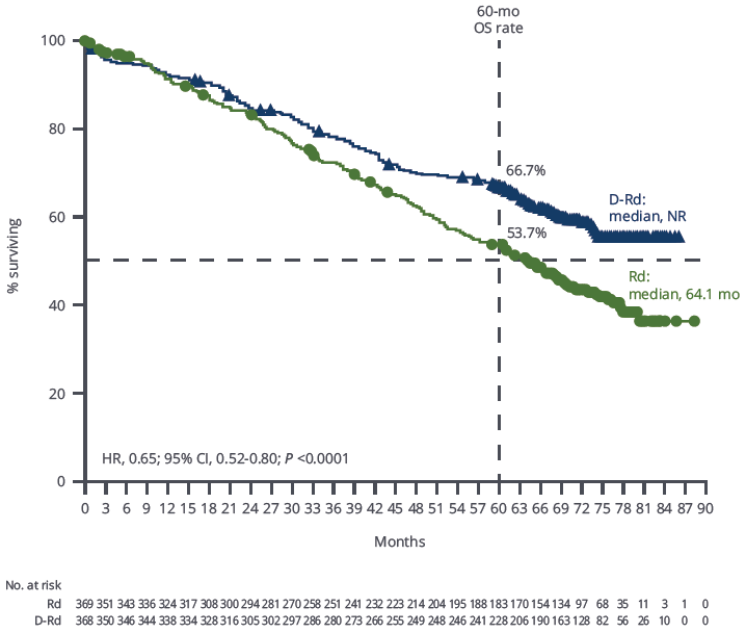
FIGURE 2: OS with D-VMP and VMP in the ITT population



Mateos MV et al ASH 2022.

MAIA

FIGURE 2: OS with D-Rd and Rd in the ITT population[a]



Kumar et al. ASH 2022

Analysis of OS in Pre-specified Patient Subgroups

ALCYONE

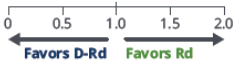
FIGURE 3: Analysis of OS in pre-specified patient subgroups

	D-VMP		VMP		
	n/N	*Median OS (mo)*	*n/N*	*Median OS (mo)*	HR (95% CI)[a]
Sex					
Male	78/160	72.7	94/167	50.7	0.70 (0.52-0.95)
Female	82/190	83.0	113/189	55.1	0.60 (0.45-0.79)
Age					
<75 years	105/246	85.5	137/249	56.6	0.62 (0.48-0.80)
≥75 years	55/104	59.1	70/107	49.7	0.71 (0.50-1.01)
Race					
White	142/297	81.0	182/304	52.9	0.66 (0.53-0.82)
Other	18/53	NE	25/52	78.1	0.55 (0.30-1.01)
Region					
Europe	137/289	82.2	177/295	53.6	0.66 (0.53-0.83)
Other	23/61	NE	30/61	57.9	0.57 (0.33-0.98)
Baseline renal function (CrCl)					
>60 mL/min	92/200	83.0	113/211	57.9	0.71 (0.54-0.94)
≤60 mL/min	68/150	79.2	94/145	48.1	0.55 (0.40-0.76)
Baseline hepatic function					
Normal	140/301	82.2	173/303	55.7	0.68 (0.54-0.85)
Impaired	20/46	NE	34/52	40.7	0.51 (0.29-0.89)
ISS disease stage					
I	18/69	NE	26/67	NE	0.52 (0.29-0.96)
II	63/139	83.0	88/160	61.3	0.72 (0.52-1.00)
III	79/142	63.0	93/129	42.3	0.57 (0.42-0.78)
Type of MM					
IgG	98/207	81.0	124/218	58.2	0.71 (0.54-0.92)
Non-IgG	43/82	72.5	51/83	46.2	0.67 (0.45-1.01)
Cytogenetic risk at study entry					
High risk[b]	33/53	46.2	31/45	39.5	0.85 (0.52-1.38)
Standard risk	113/261	83.0	149/257	55.1	0.58 (0.45-0.74)
ECOG PS score					
0	22/78	NE	55/99	53.7	0.35 (0.21-0.57)
1-2	138/272	72.5	152/257	52.9	0.73 (0.58-0.92)

MAIA

FIGURE 3: Analysis of OS in pre-specified patient subgroups[a]

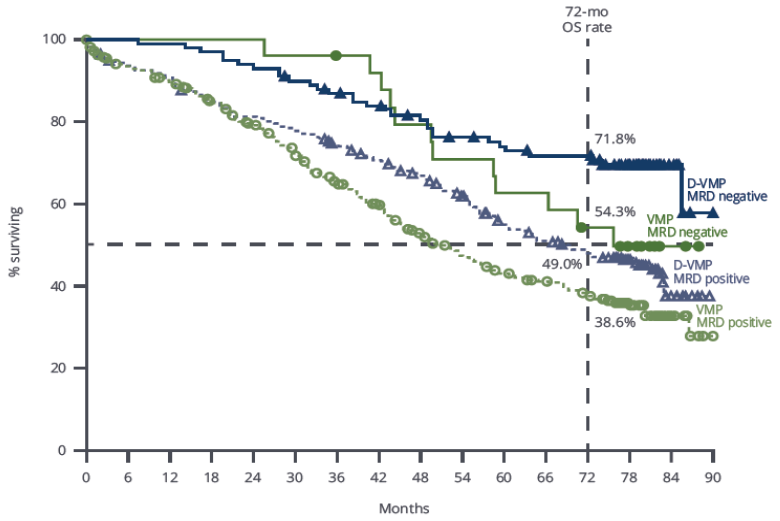
	D-Rd		Rd		
	n/N	*Median OS (mo)*	*n/N*	*Median OS (mo)*	HR (95% CI)[b]
Sex					
Male	86/189	NE	114/195	60.6	0.70 (0.53-0.93)
Female	64/179	NE	88/174	67.8	0.62 (0.45-0.85)
Age					
<75 years	71/208	NE	101/208	77.6	0.64 (0.47-0.86)
≥75 years	79/160	73.5	101/161	54.8	0.67 (0.50-0.90)
Race					
White	138/336	NE	181/339	65.4	0.69 (0.55-0.86)
Other	12/32	NE	21/30	49.1	0.43 (0.21-0.88)
Region					
North America	40/101	NE	61/102	54.8	0.54 (0.36-0.80)
Other	110/267	NE	141/267	66.4	0.71 (0.55-0.91)
Baseline renal function (CrCl)					
>60 mL/min	83/206	NE	113/227	69.7	0.72 (0.55-0.96)
≤60 mL/min	67/162	NE	89/142	54.8	0.56 (0.41-0.77)
Baseline hepatic function					
Normal	132/335	NE	188/340	63.8	0.62 (0.49-0.77)
Impaired	18/31	63.5	14/29	73.8	1.29 (0.64-2.60)
ISS disease stage					
I	28/98	NE	36/103	NE	0.78 (0.48-1.28)
II	64/163	NE	88/156	61.7	0.59 (0.43-0.81)
III	58/107	65.2	78/110	47.3	0.66 (0.47-0.93)
Type of MM					
IgG	93/225	NE	120/231	68.6	0.74 (0.56-0.97)
Non-IgG	29/74	NE	46/76	53.7	0.54 (0.34-0.85)
Cytogenetic risk at study entry					
High risk[c]	28/48	55.6	36/44	42.5	0.65 (0.39-1.06)
Standard risk	105/271	NE	147/279	65.5	0.64 (0.50-0.82)
ECOG PS score					
0	37/127	NE	49/123	NE	0.69 (0.45-1.06)
1	76/178	NE	110/187	58.3	0.62 (0.47-0.84)
≥2	37/63	61.9	43/59	39.0	0.64 (0.41-1.00)



OS by MRD Status

ALCYONE

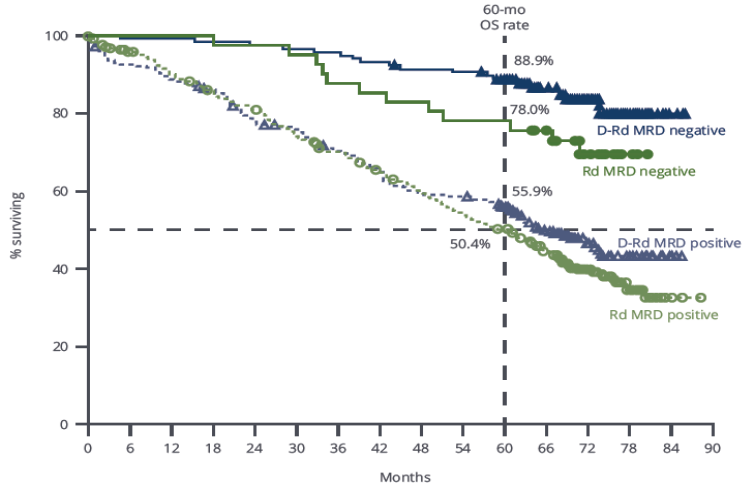
FIGURE 4: OS by MRD status[a]



No. at risk																
VMP MRD negative	25	25	25	25	25	24	23	22	19	17	15	15	12	9	3	0
D-VMP MRD negative	99	99	98	96	92	88	84	80	76	70	67	64	64	45	10	0
VMP MRD positive	331	299	286	266	243	218	193	175	148	131	118	109	100	61	12	0
D-VMP MRD positive	251	228	220	205	196	187	174	164	151	135	116	106	98	67	14	0

MAIA

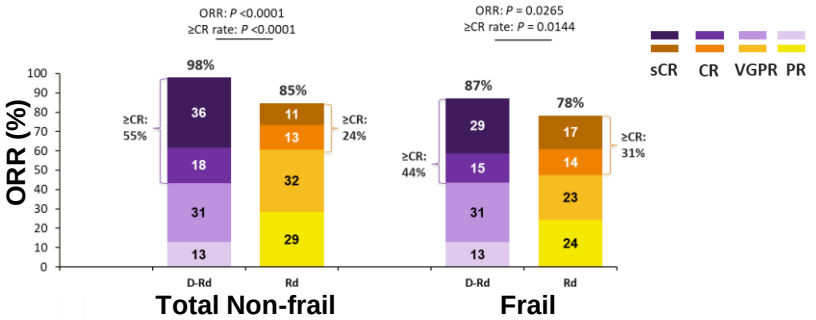
FIGURE 4: OS by MRD status[a,b]



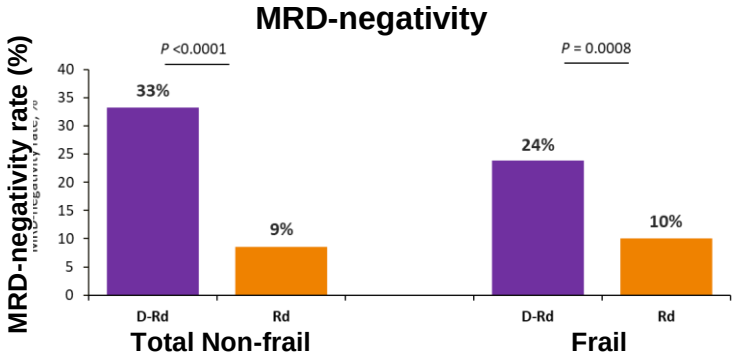
No. at risk																
Rd MRD negative	41	41	41	41	40	39	36	35	34	32	32	29	14	3	0	0
D-Rd MRD negative	118	117	117	116	115	114	113	110	107	106	99	86	55	22	3	0
Rd MRD positive	328	302	283	267	254	231	215	197	180	163	151	125	83	32	3	0
D-Rd MRD positive	250	229	221	212	190	183	167	156	142	140	129	104	73	34	7	0

Daratumumab plus lenalidomide and dexamethasone (D-Rd) vs lenalidomide and dexamethasone (Rd) in transplant-ineligible newly diagnosed multiple myeloma (NDMM): frailty subgroup analysis of MAIA

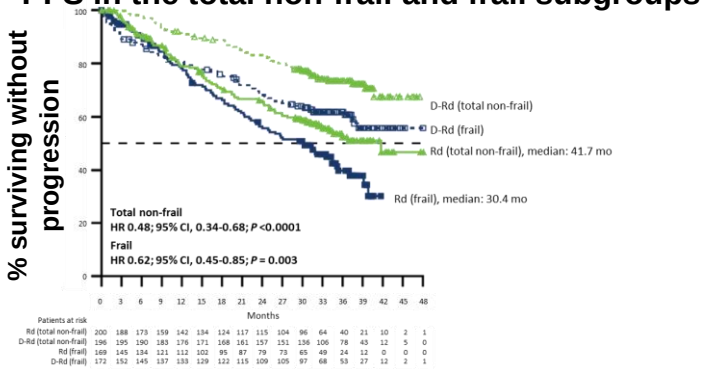
ORR and ≥CR rate



MRD-negativity



PFS in the total non-frail and frail subgroups



Safety

	Total Non-frail (n=395)		Frail (n=334)	
n (%)	D-Rd (n=196)	Rd (n=199)	D-Rd (n=168)	Rd (n=166)
Patients with a TEAE with outcome of death	7 (4)	7 (4)	20 (12)	20 (12)
Patients with a serious TEAE	123 (63)	126 (63)	125 (74)	121 (73)
Treatment discontinuations due to TEAEs	13 (7)	31 (16)	17 (10)	32 (19)
Deaths	26 (13)	46 (23)	57 (34)	57 (34)

Our findings, although based on a retrospective assessment of frailty, support the clinical benefit of D-Rd in patients with transplant-ineligible NDMM enrolled in MAIA, regardless of frailty status

Facon et al. Leukemia published online Jan 2, 2022

VRD- A SOC for those who do not have access to CD38 ?
SWOG 0777: PFS with RVd versus Rd

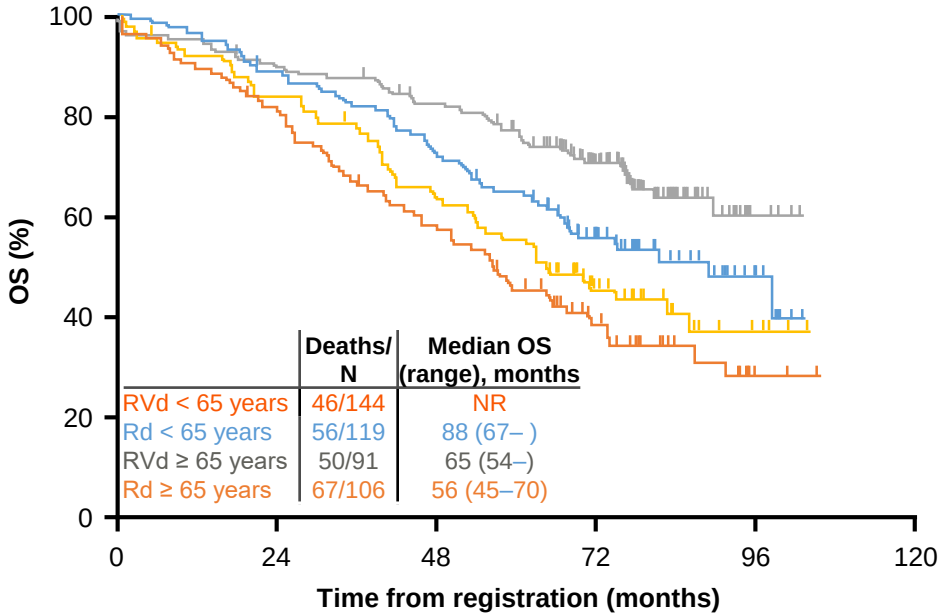
Median PFS (months)[1]

Age (years)	RVd	Rd
< 65	48	34
≥ 65	34	24
> 75	34	17

Long term FU[2]

OS in pts ≥ 65 years: HR 0.769, p 0.168

OS by age[1]

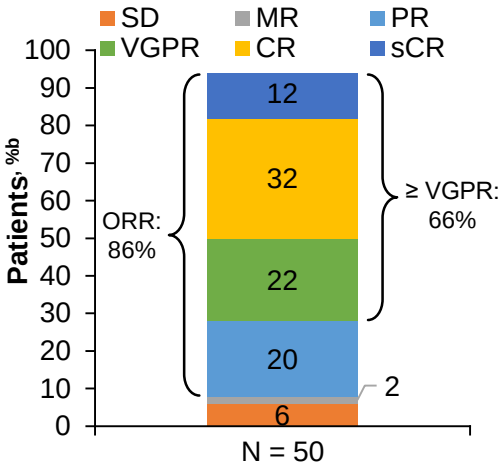


1. Durie B et al. Blood 2018;132:1992; 2. Durie B et al. Blood Cancer J 2020;10:53

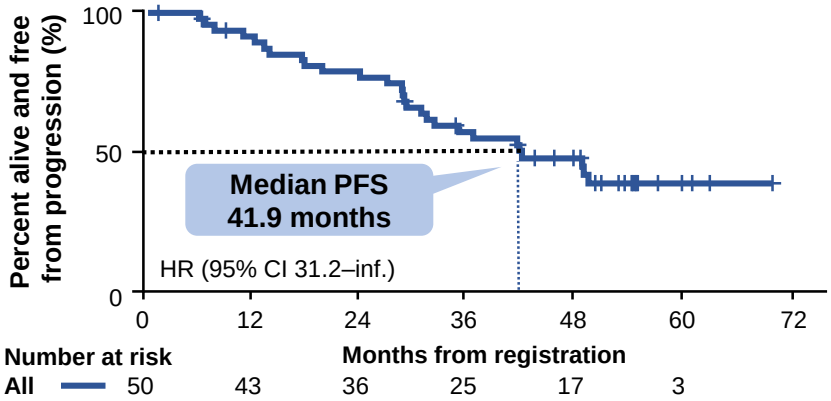
Modified RVd (RVd-lite) in TNE Patients

Baseline characteristics	N = 50
Median age, years (range)	73 (65–91)
ISS stage at diagnosis, %	
I	38
II	34
III	28
ECOG PS score, %	
0	50
1	36
2	14

Response rate



PFS



≥ CR was 44% (ITT population; N = 50)
ORR was 86%; ≥ VGPR was 66% for patients evaluable for response[a] after 4 cycles (n = 46)
Median TTR was 1.1 months

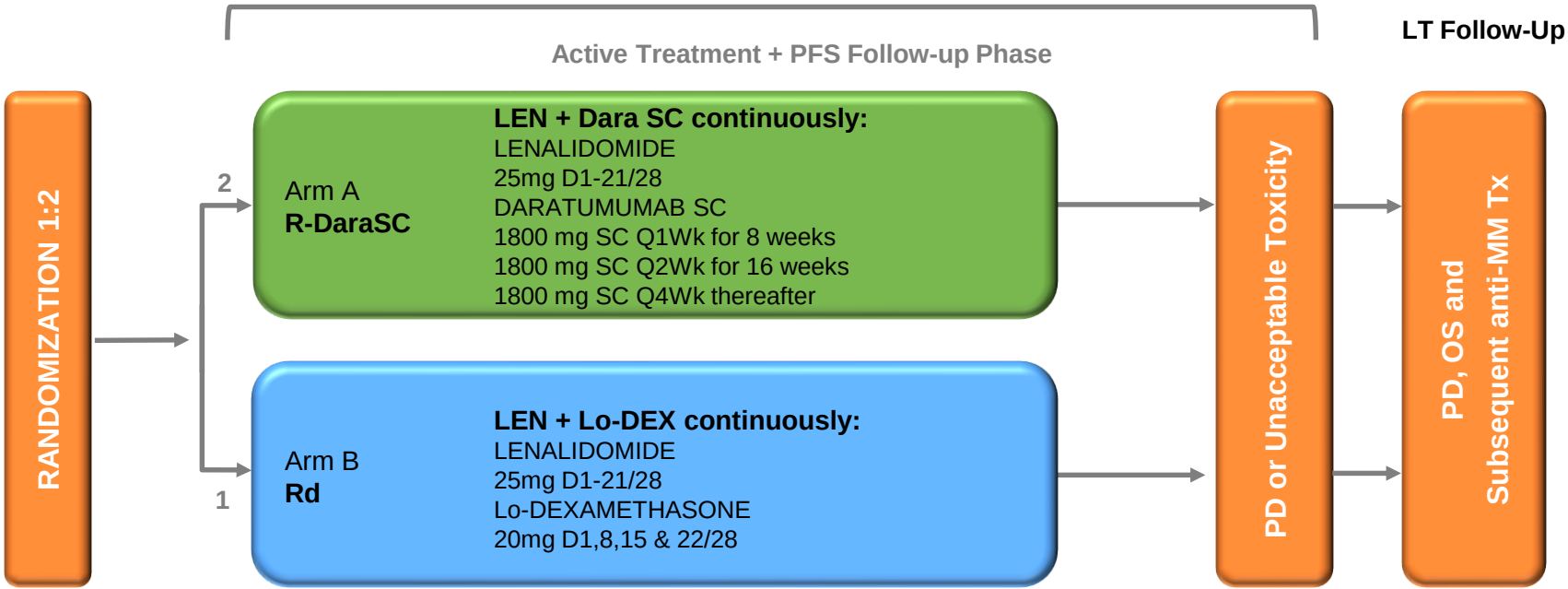
Grade 3 or 4 AEs of interest:
- Peripheral neuropathy (2%), neutropenia (14%)

RVd-lite is Investigational only, not approved.
[a] The first 10 patients received bortezomib i.v. for cycle 1 only followed by s.c. administration; subsequent patients received bortezomib s.c.; [b] 6% of patients received < 4 cycles of therapy and were therefore not evaluable.
AE, adverse event; CR, complete response; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance status; ISS, International Staging System; MR, minimal response; ORR, overall response rate; PFS, progression-free survival; R, lenalidomide; sCR, stringent complete response; TTR, time to response; V, bortezomib; VGPR, very good partial response

O'Donnell EK et al. Br J Haematol 2018;182:222-30.
O'Donnell EK et al. ASH 2019; abstract 3178.

Discontinuation Strategies (1)

IFM 2017-03 for frail NDMM patients - A dexamethasone sparing study



Randomization will be stratified by International Staging System (I vs II vs III) and age (<80 vs ≥80

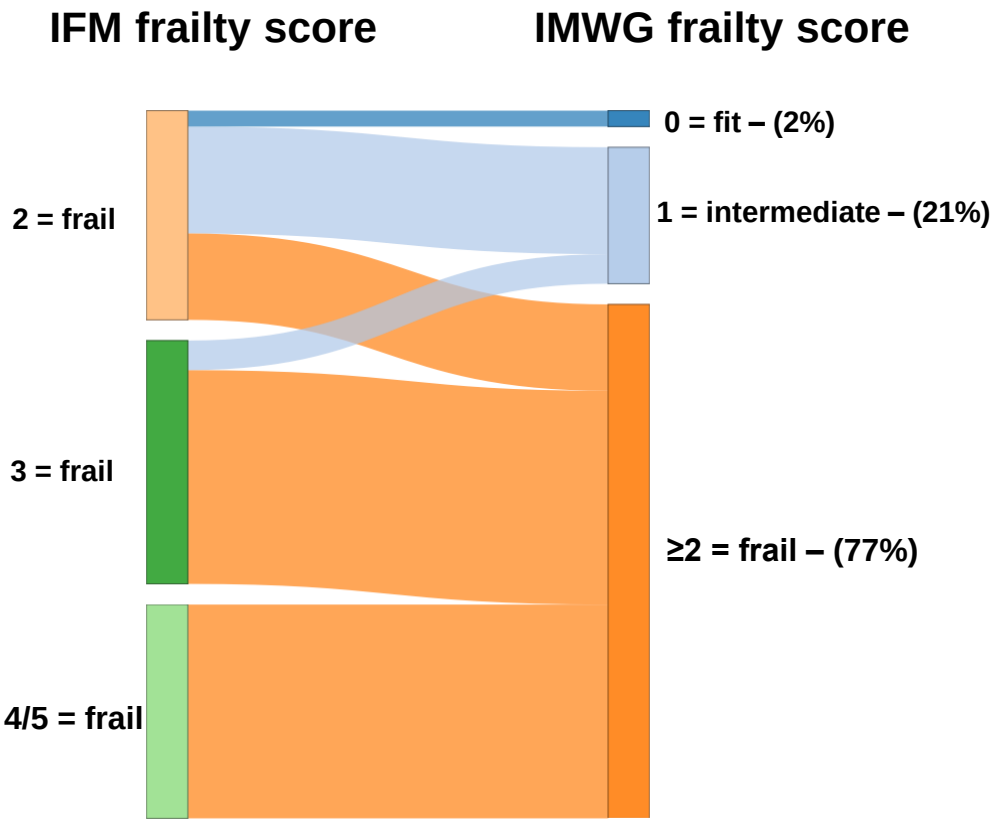
In Arm A low-dose dex (20mg/week) during Cycle 1 and 2 then methylprednisolone (with SC dara)

LT, long term; OS, overall survival; PD, progressive disease;
PFS, progression-free survival; Q, every; SC, subcutaneous; Tx, treatment

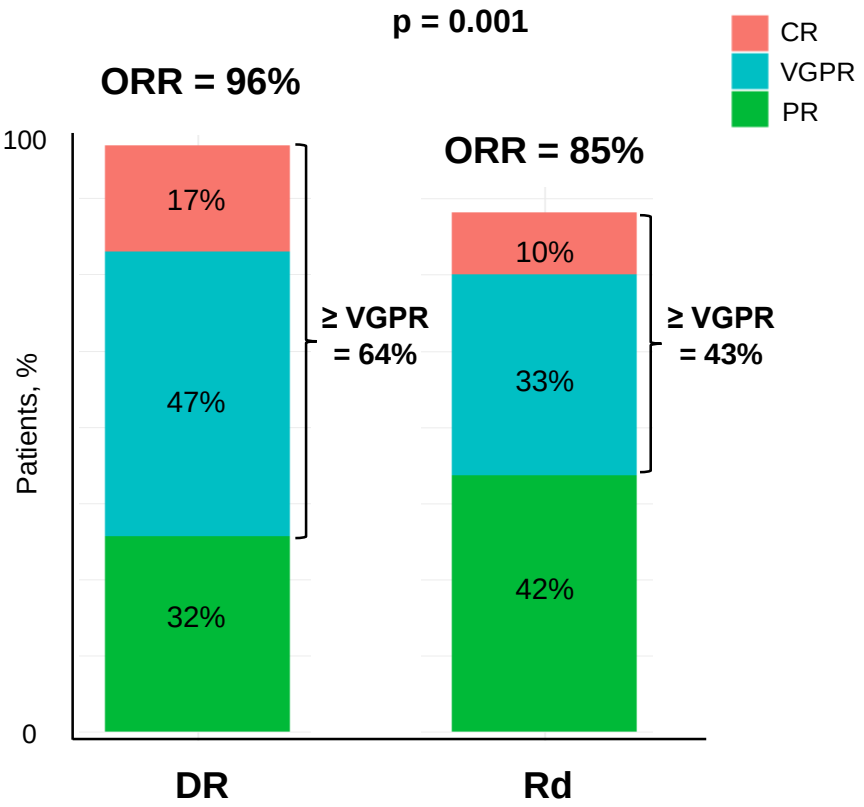
https://clinicaltrials.gov/ct2/show/NCT03993912 Manier et al ASH 2022

IFM 2017-03 – Patients characteristics

Characteristics	DR group (N=199)	Rd group (N=94)
Median age (range) - yr	81 (68-92)	81 (68-90)
Age category – no. (%)		
65 to < 70 yr	2 (1%)	2 (2%)
70 to < 75 yr	30 (15%)	13 (14%)
75 to < 80 yr	49 (25%)	19 (20%)
≥ 80 yr	118 (59%)	61(65%)
Sex - no. (%)		
Female	101 (51%)	48 (51%)
Male	98 (49%)	46 (49%)
ECOG – no. (%)		
0	21 (10%)	9 (10%)
1	93 (46%)	47 (50%)
2	86 (44%)	38 (40%)
Charlson – no. (%)		
≤ 1	113 (58%)	57 (61%)
> 1	87 (42%)	37 (39%)
IFM frailty score – no. (%)		
≤ 1	0	0
2	57 (29%)	35 (37%)
3	81 (41%)	26 (28%)
4	44 (22%)	24 (26%)
5	17 (9%)	9 (10%)



IFM 2017-03 – Best response rate

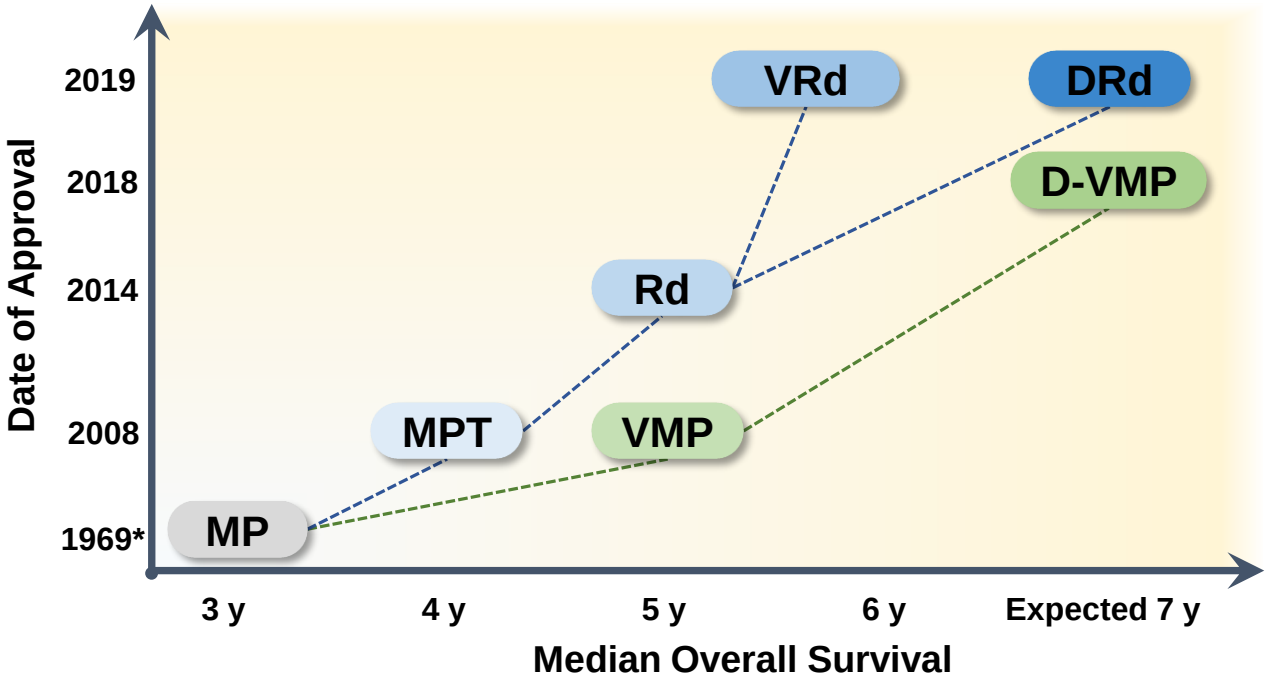


IFM 2017-03 – Most common grade ≥3 AEs

	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			
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

Treatment Landscape and Perspective in Newly Diagnosed Transplant-Ineligible Patients: Regimens, Date of Approval (EMA), and Overall Survival



Treatment perspectives

New drugs/strategies/studies

- Dara-/Isa-VRd†
- New IMiDs/CELMoDs
- Bispecific antibodies
- CAR-T cells

Some key remaining topics

- Infection
- Role of MRD
- Continuous or fixed-duration therapy

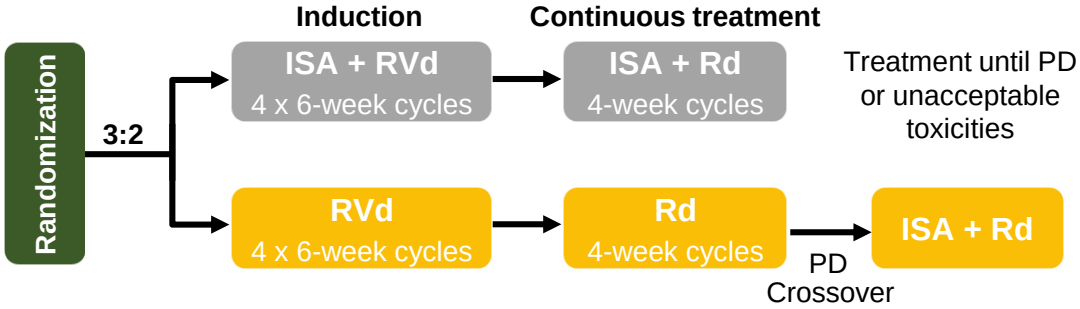
*Publication date, not an approval date; †NCT03319667 and NCT03652064.

CAR-T, chimeric antigen receptor T cell; Dara, daratumumab; DRd, daratumumab-lenalidomide-dexamethasone; D-VMP, daratumumab plus bortezomib-melphalan-prednisone; EMA, European Medicines Agency; IMiD, immunomodulatory drug; Isa, isatuximab; MP, melphalan-prednisone; MPT, melphalan-prednisone-thalidomide; MRD, minimal residual disease; Rd, lenalidomide-dexamethasone; VMP, bortezomib-melphalan-prednisone; VRd, bortezomib-lenalidomide-dexamethasone.

Facon, Leleu, Manier, Blood 2023 in press

IMROZ (EFC12522) and CEPHEUS (MMY3019): study designs

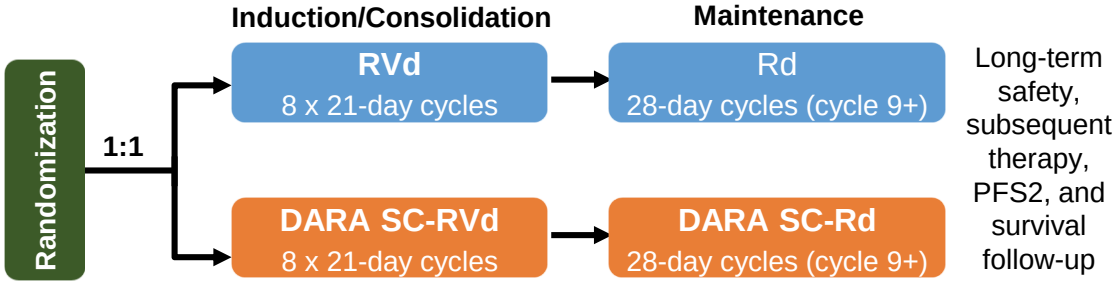
IMROZ[1]: NDMM patients ineligible for HDT-ASCT (N = 440)



Primary endpoint:
- PFS (40 months vs 62.5 months)

Secondary endpoints:
- OS, PFS2
- ORR, CR
- Safety, QoL
- MRD

CEPHEUS[2]: phase 3 study of DARA SC-RVd vs RVd in transplant-ineligible FLMM (N = 360)



Primary endpoint:
- MRD

Secondary endpoints:
- PFS, OS
- Durable MRD
- ORR, VGPR, CR
- PFS2

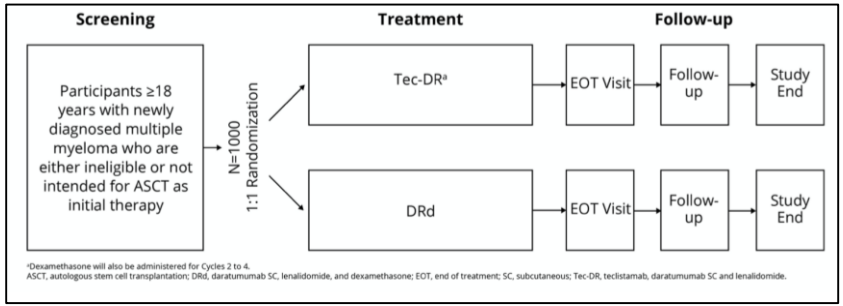
No cross-trial comparison is intended with this data.

CR, complete response; d, dexamethasone; HDT-ASCT, high-dose therapy and autologous stem cell transplantation; ISA, isatuximab; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, lenalidomide; SC subcutaneous; VGPR, very good partial response; V, bortezomib

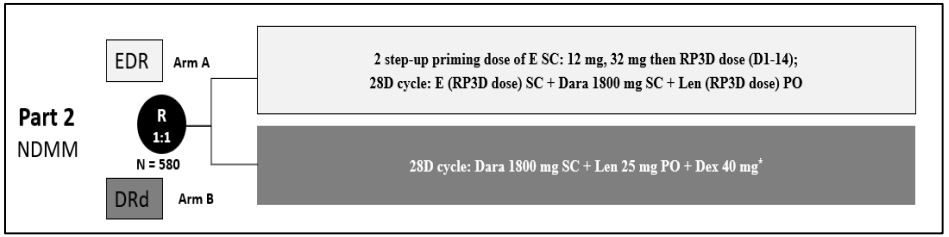
1. Available from: https://clinicaltrials.gov/ct2/show/NCT03319667. Accessed June 2019.
2. Available from: https://clinicaltrials.gov/ct2/show/NCT03652064. Accessed June 2019.

Frontline immunotherapies for TNE MM Patients

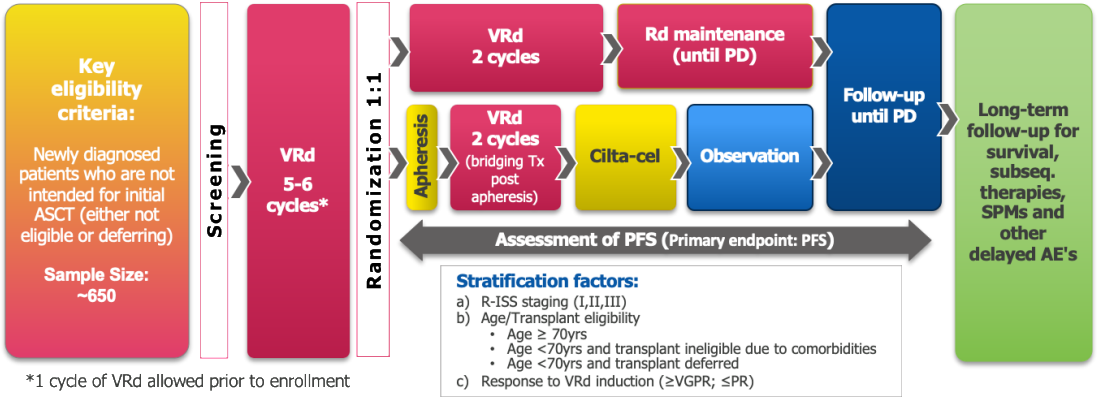
MajesTEC-7



MagnetisMM-6



CARTITUDE-5



Conclusion

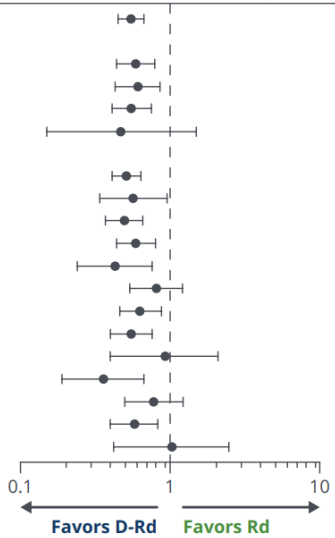
- CD38 Abs- containing regimens are now SOC for elderly patients with NDMM.
- DRd is currently the most effective regimen and has an acceptable safety profile including for frail patients
- VRD remains a SOC if there is no access to CD38 Abs.
- Excluding patients from receiving CD38 Abs-based immunotherapy because of age and/or frailty is questionable because CD38 Abs are effective, manageable, and improve QoL.
- Planned/Ongoing studies investigating CART and Bispecific Abs

MAIA - Subgroup Analysis of PFS

- A total of 737 patients were randomly assigned to either D-Rd (n = 368) or Rd (n = 369) and were included in the intent-to-treat (ITT) population
- Most subgroups had a similar number of patients in each treatment arm
- After a median follow-up of 64.5 months, PFS favored D-Rd versus Rd in most subgroups (**Figure 1**)

FIGURE 1: Subgroup analysis of PFS in the ITT population

	D-Rd		Rd		HR (95% CI)[a]
	n/N	*Median PFS (mo)*	*n/N*	*Median PFS (mo)*	
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)

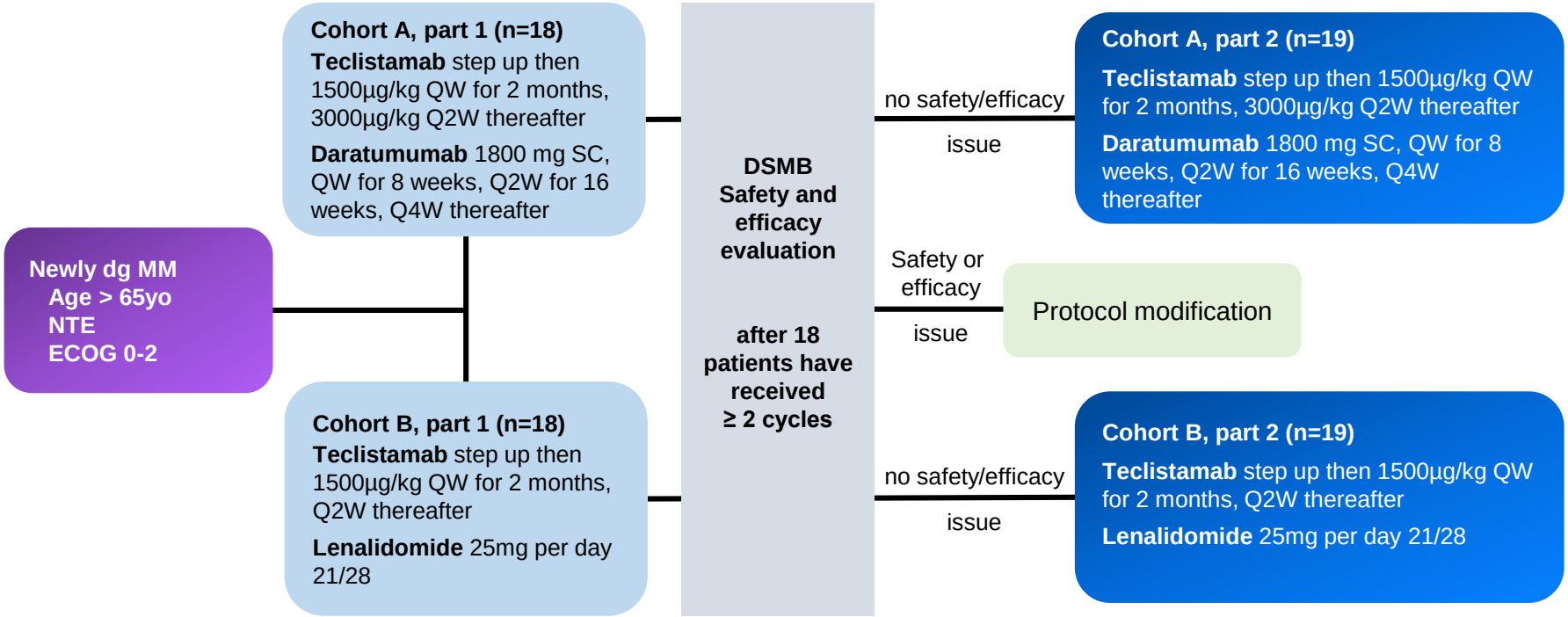


PFS, progression-free survival; ITT, intent-to-treat; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; ISS, International Staging System; NR, not reached; HRCA, high-risk cytogenetic abnormality.

[a]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. HR <1 indicates an advantage for D-Rd.

IFM 2021-01 – study design

Phase 2

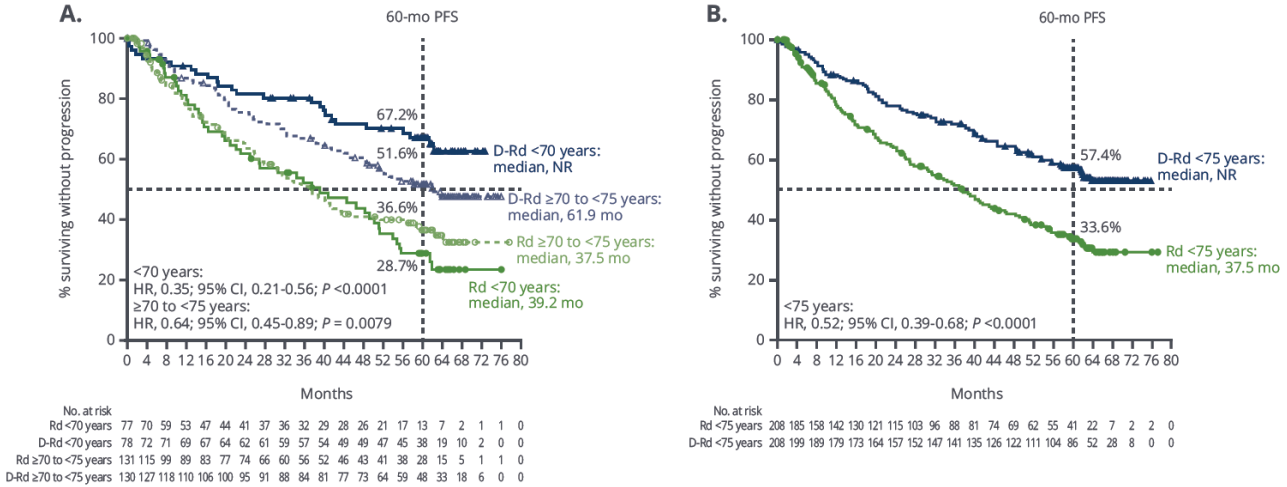


≥ 30% CRS grade ≥ 3
≥ 50% infection grade ≥ 3 (except COVID)
ORR ≤ 50%

PFS in MAIA, patients < 70 y

- The PFS benefit of D-Rd versus Rd was most pronounced in the subgroup of patients aged <70 years

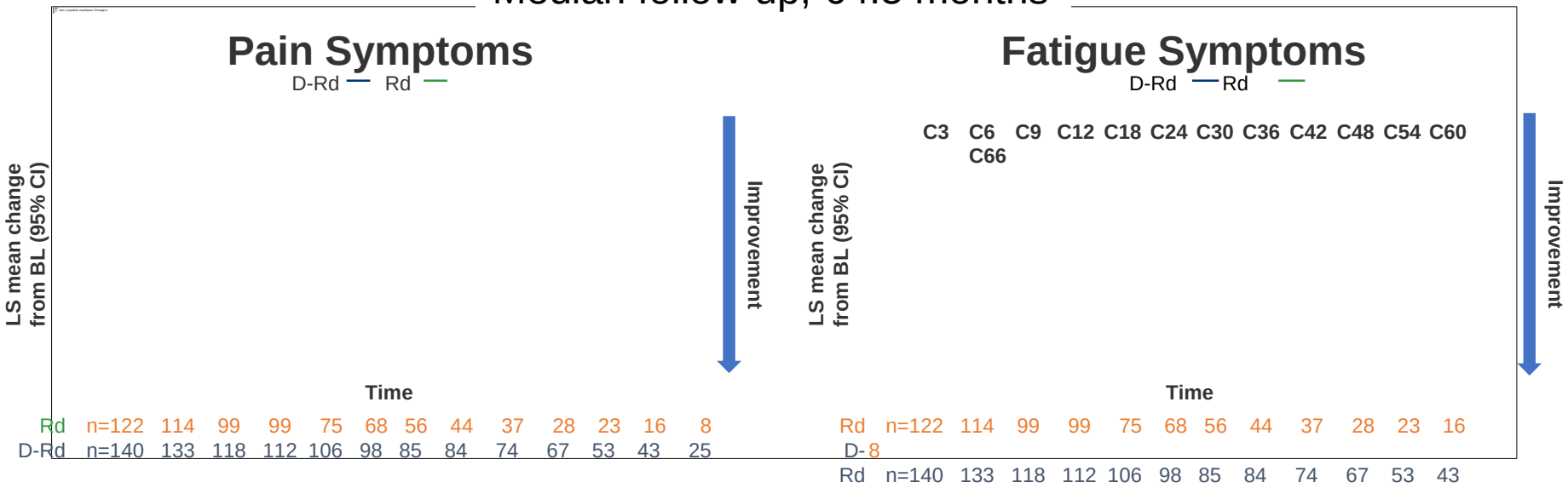
FIGURE 1: PFS with D-Rd and Rd for (A) subgroups of patients aged <70 years and ≥70 to <75 years and (B) the overall subgroup of patients aged <75 years



Facon et al. ASH 2022

MAIA: LS Mean Change From Baseline in EORTC QLQ-C30 Scores Over Time in Frail TNE Patients With NDMM

Median follow-up, 64.5 months



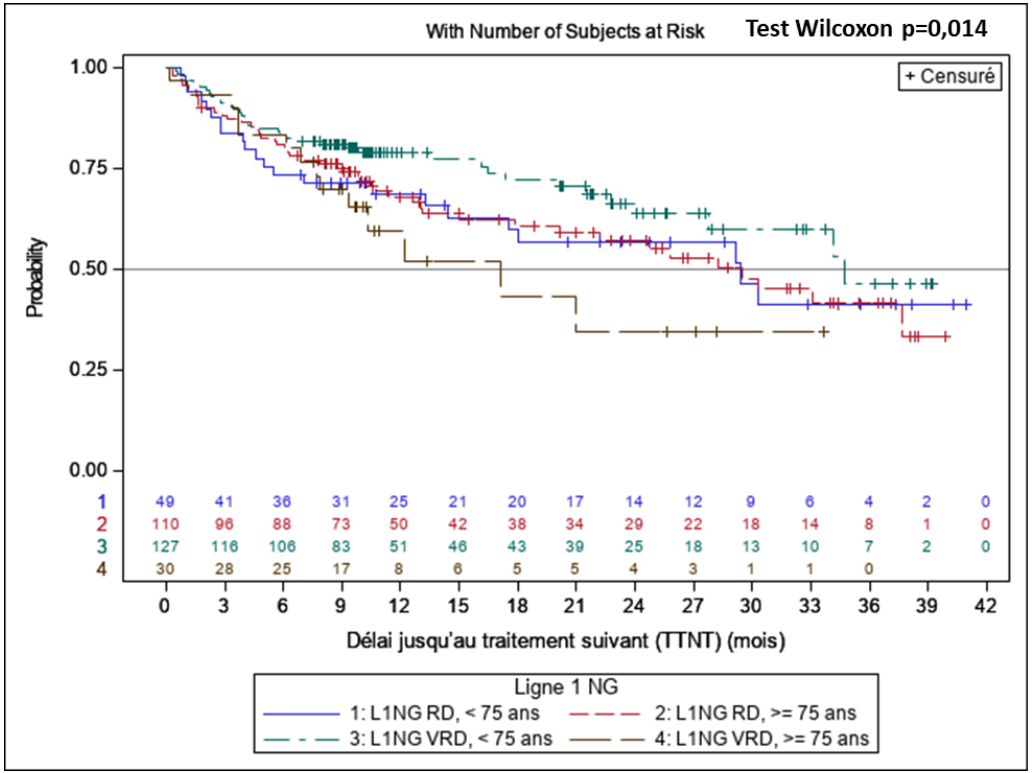
More patients remained on D-Rd vs Rd after cycle 42

- Patients treated with D-Rd showed large reductions in pain from baseline (≥20-point change)
- Pain symptoms improved more with D-Rd vs Rd

- Fatigue moderately improved with D-Rd and Rd
- The triplet regimen D-Rd did not increase fatigue

Perrot et al. ASH 2022 oral presentation

VRd or Rd in L1 – TNT according to age
RWE – IFM real life registry



TNT median, months

- **Rd**
  - 29.4 mo. [14,4-ND] < 75 y (n=50)
  - 29.5 mo. [20,1-ND] ≥ 75 y (n=110)
- **VRd**
  - 34.7 mo. [27,8 ND] <75 y (n=127)
  - 17.1 mo. [9,3-ND] ≥ 75 y (n=30)