

Transplant ineligible patients

סדנת מתמחים 2025

דר' מירי זקצר

מרכז רפואי סורוקה

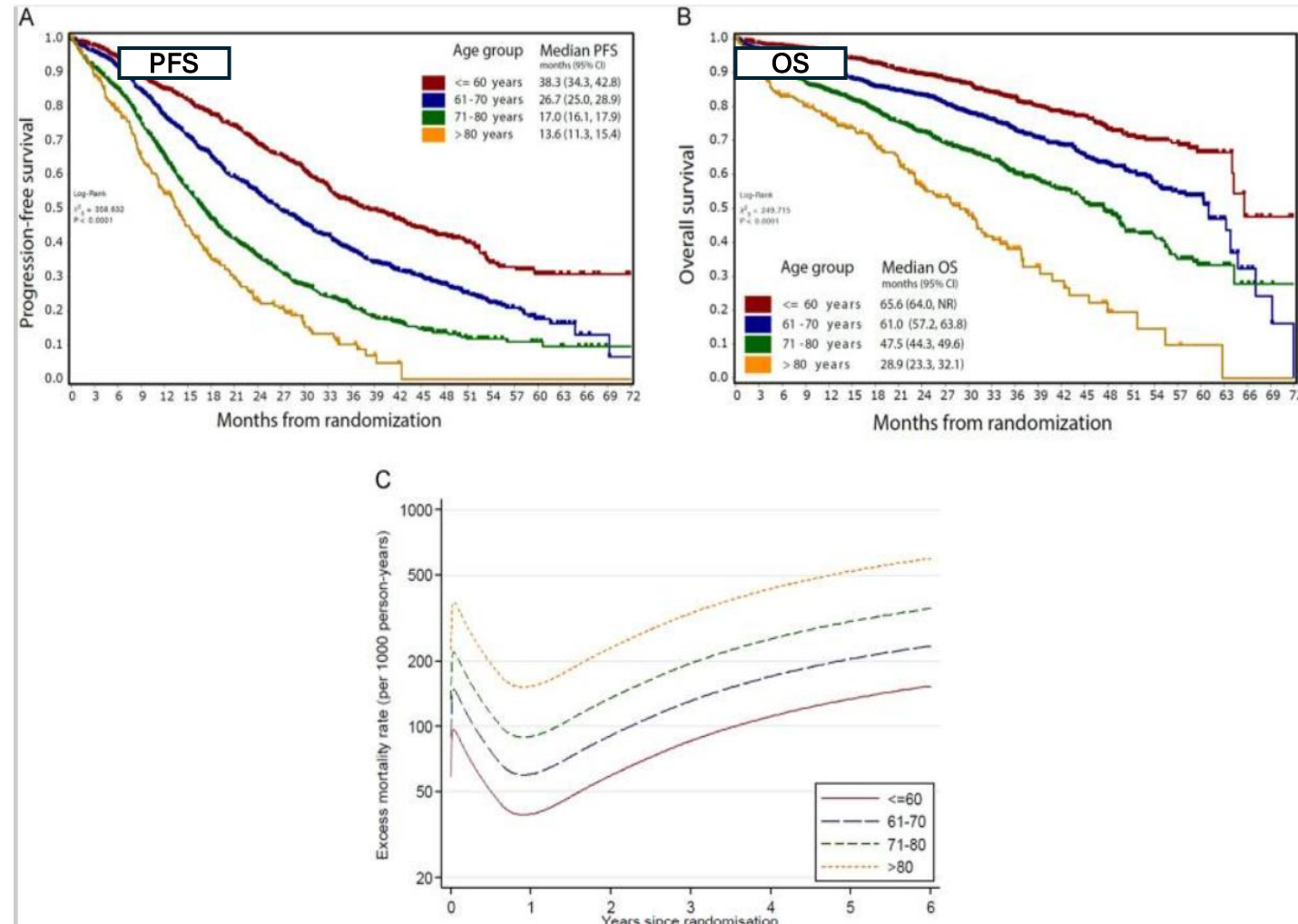
Agenda

- Multiple myeloma in elderly- characteristics
- Frailty score
- Treatment for MM in transplant ineligible

- MM effects mostly elderly pt. median age 69
- 33% of the MM pt. are ≥ 75 , 10% >age 80
- Duration of survival has improved dramatically in the last 20 years, but older adult < young pt.

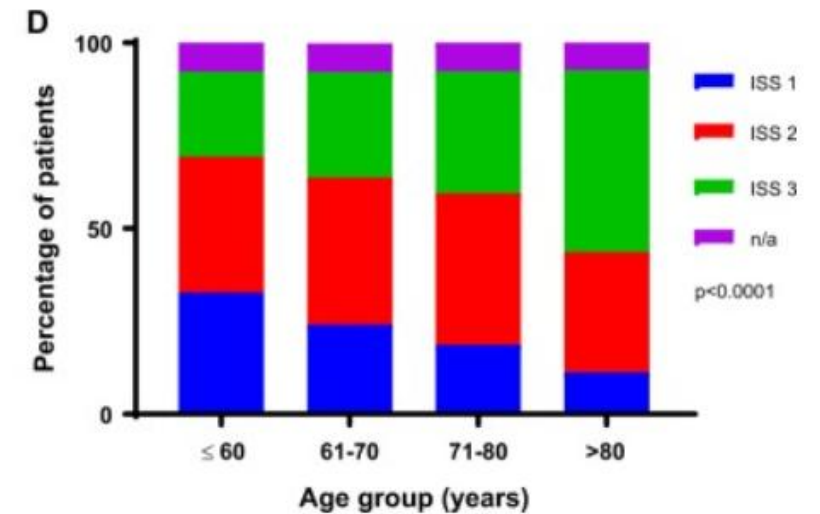
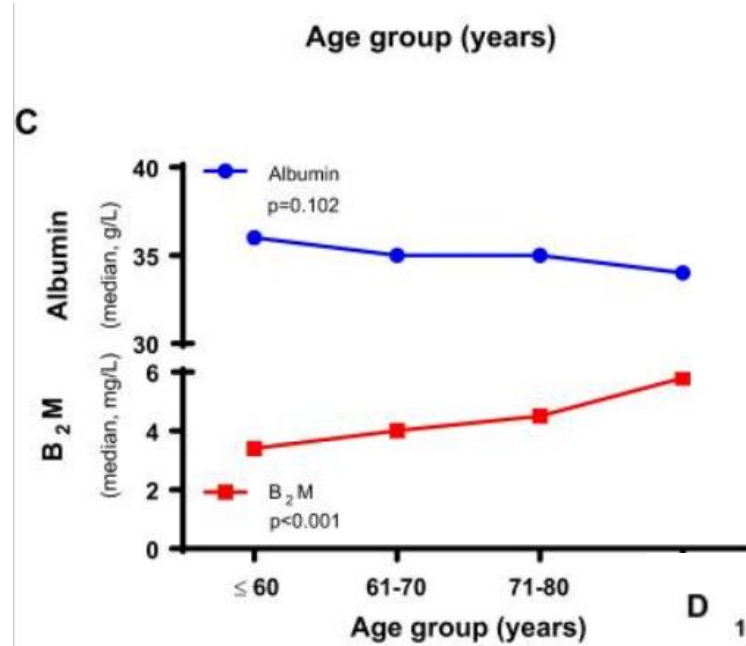
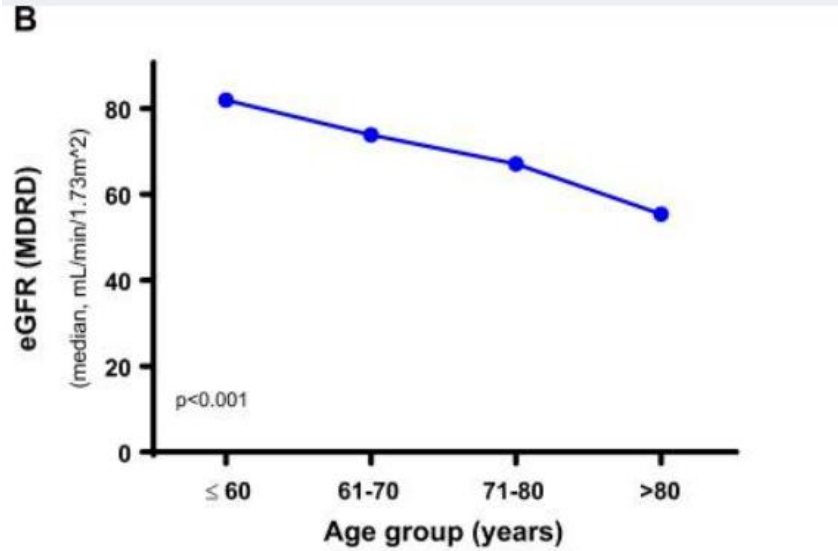
Older age- worse outcome :OS, PFS, early mortality

Myeloma XI trial¹



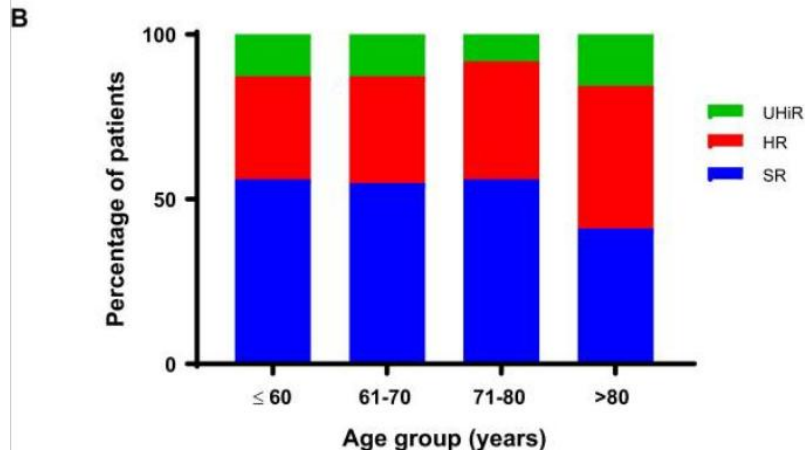
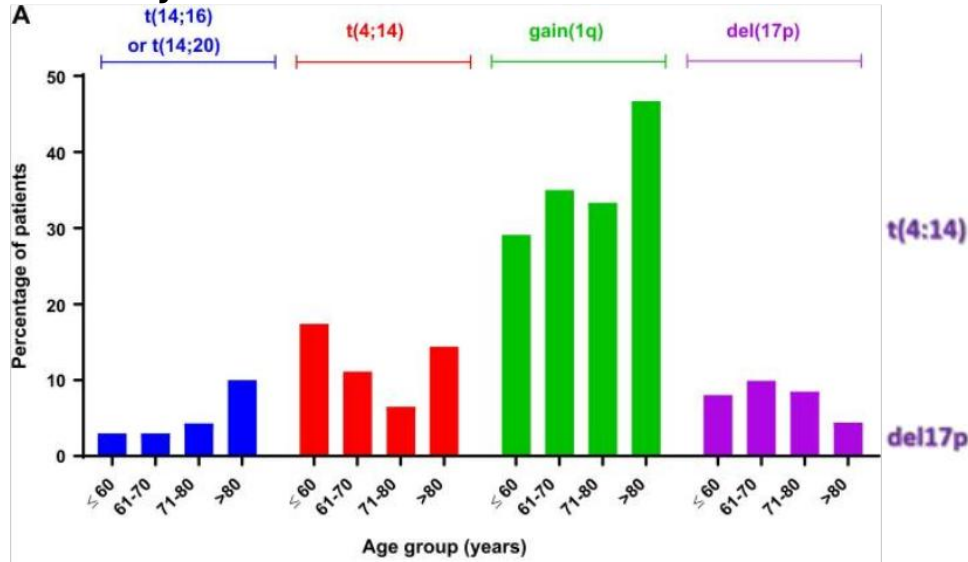
1. Pawlyn et al.; Leukemia.;34(2):604-612.

Myeloma characteristics in elderly

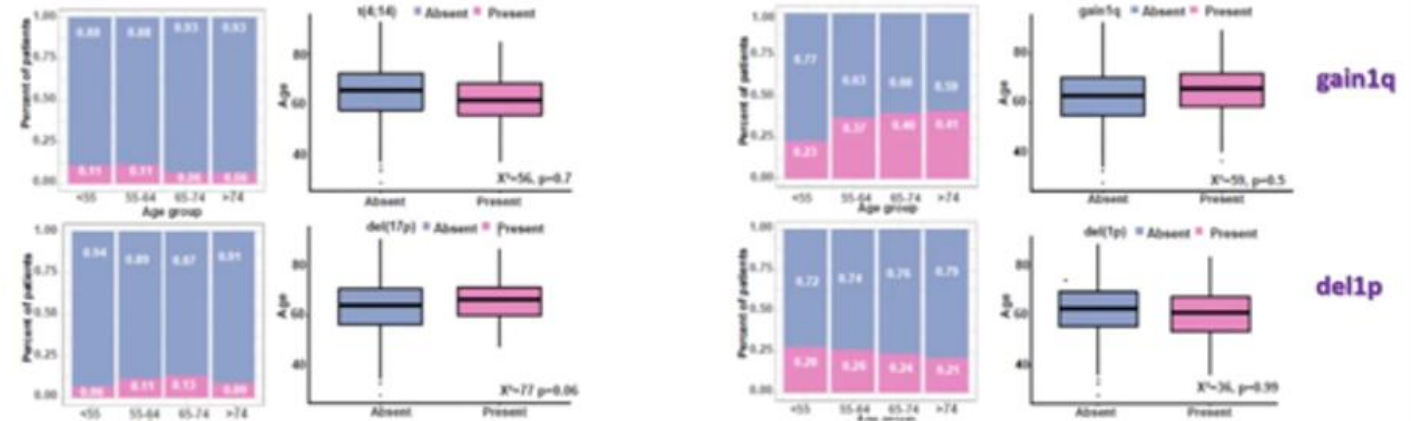


Cytogenetic characteristics

Myeloma XI trial¹



CoMMpass study²



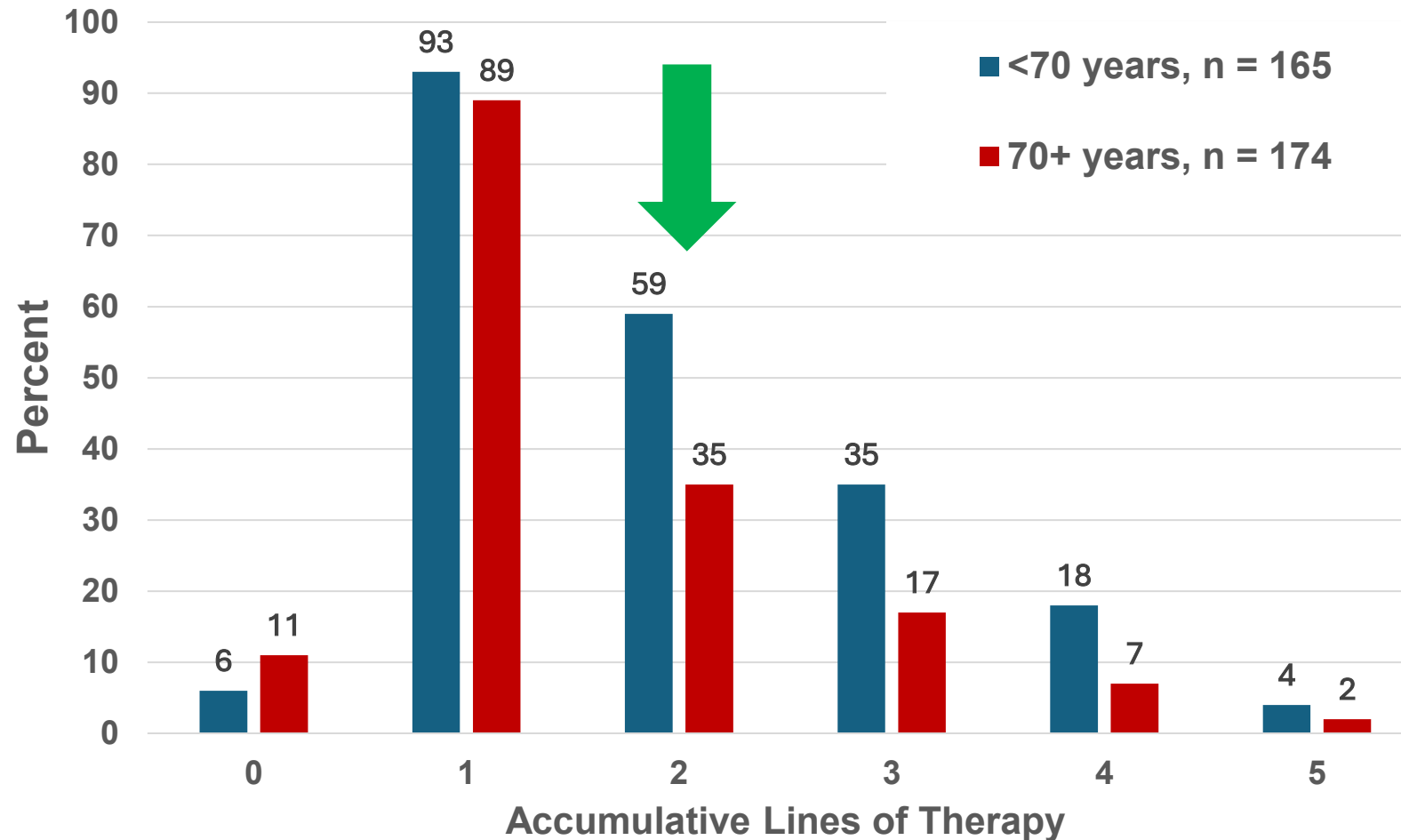
Similar frequency of high risk cytogenetic across all the age groups

1. Pawlyn et al; Leukemia; 34(2):604-612
 2. Boyle EM et al; Leukemia 2022; 36:221-224

Why the prognosis is worse?

1. Comorbidity
2. Physiological reserve and patient fitness
3. Immunosenescence
4. Reduced tolerance to aggressive treatments
5. Disease aggressiveness

Accumulative Lines of Therapy Received by Age at Diagnosis : Best Therapy Should Be Used Upfront in Elderly Patients



Elderly MM: Definitions

- **Transplant-ineligible patients:** Patients considered not fit enough to undergo ASCT due to age or comorbidities.
- **Elderly (older adults):** Patients aged ≥ 65 years
- **Frailty:** decline in physiological function, which leads to dependency, vulnerability and a high risk of complications resulting in an increased risk of morbidity and mortality

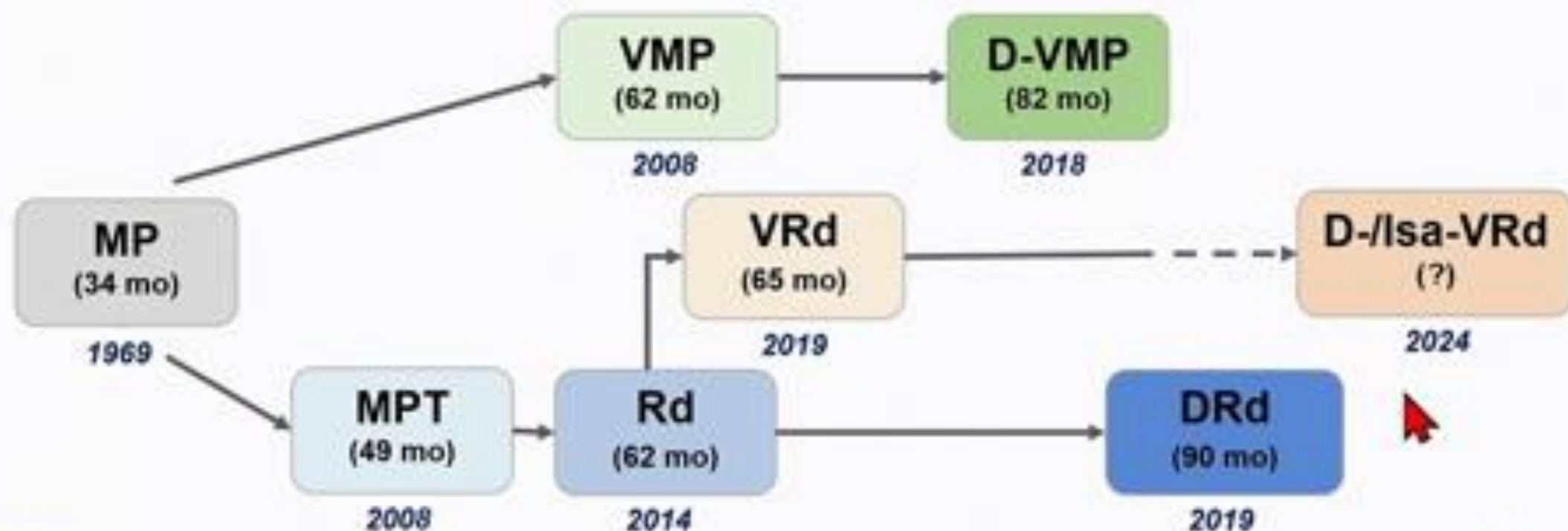
Older patients represent a heterogeneous group in which the prevalence of frailty increases with age

Frailty assessment

IMWG Frailty Score	
Category	Score
Age, y	
≤75	0
76-80	1
>80	2
Charlson Comorbidity Index	
≤1	0
≥2	1
ADL	
>4	0
≤4	1
IADL	
>5	0
≤5	1
Sum	
Fit	0
Intermediate-fit	1
Frail	≥2

Simplified IMWG	
Category	Score
Age, y	
≤75	0
76-80	1
>80	2
Charlson Comorbidity Index	
≤1	0
≥2	1
ECOG	
0	0
1	1
≥2	2
Sum	
Non-frail	0-1
Frail	≥2

Evolving treatment landscape in NDMM TNE patients



OS
(median)

3 yrs

4 yrs

5 yrs

6 yrs

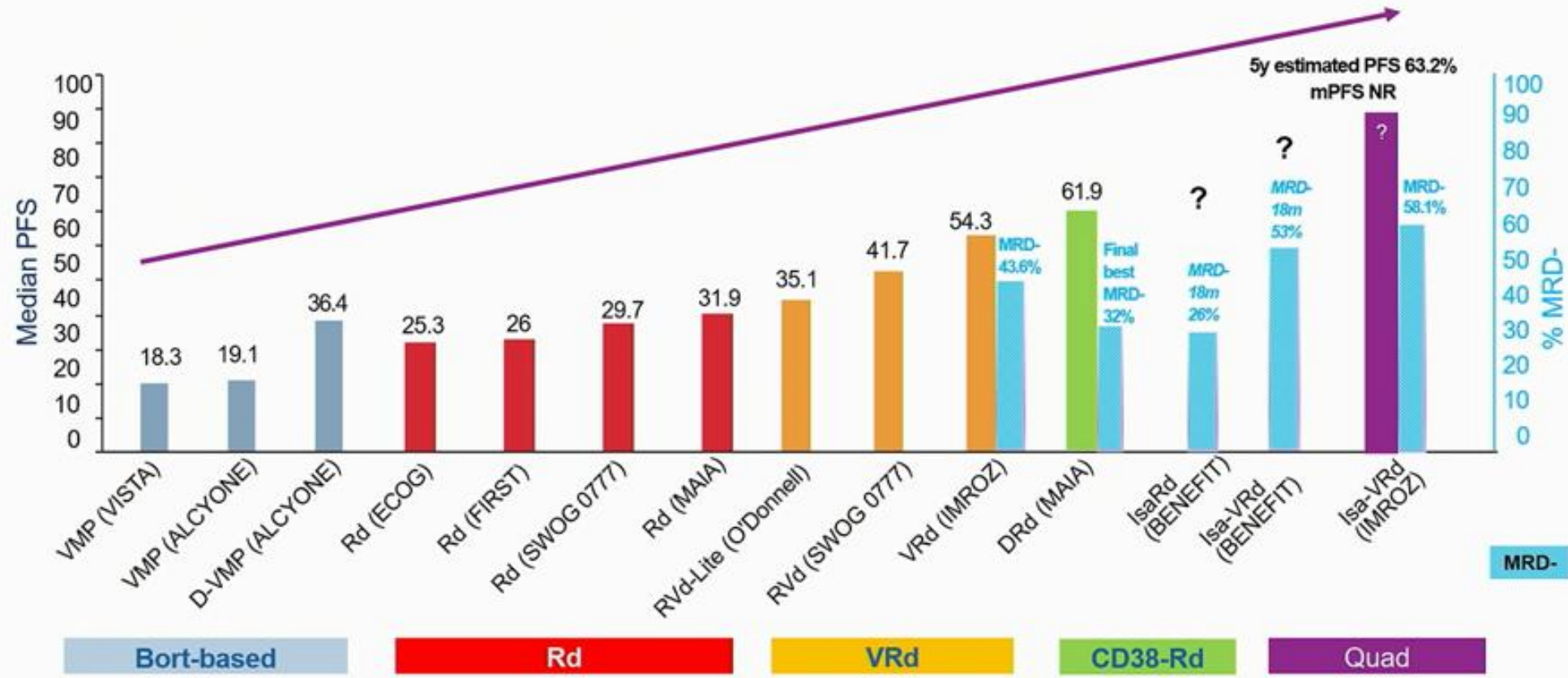
7 yrs

8 yrs

Dates of EMA approvals

Adapted from Facon, Leliu & Marier, Blood 2023

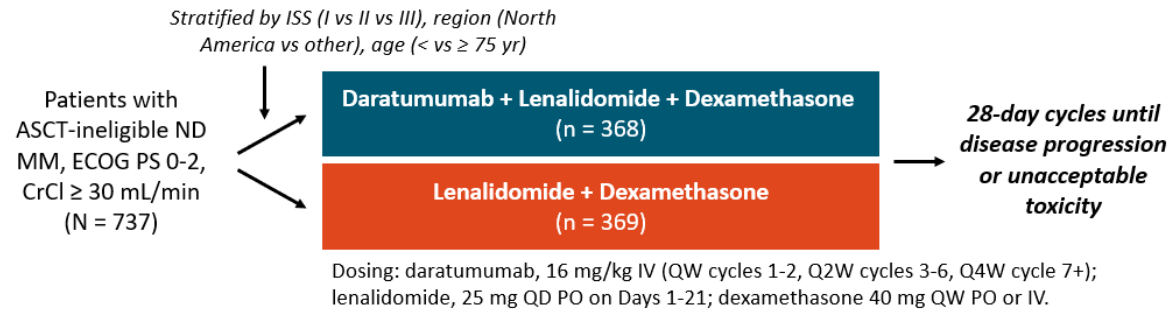
Overview of mPFS in recent phase 3 trials in transplant-ineligible NDMM



Dara backbone induction

MAIA: Dara-Rd vs Rd in ASCT-Ineligible NDMM

- Multicenter, open-label, randomized phase III trial

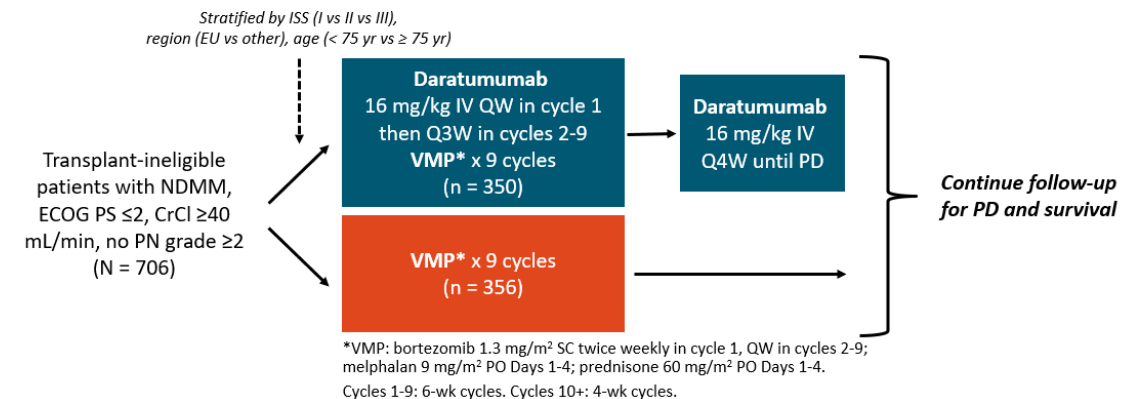


- Primary endpoint: PFS
- Secondary endpoints: TTP, CR/sCR, MRD by NGS (10^{-5}), PFS2, OS, ORR, safety

Kumar. ASH 2020. Abstr 2276. NCT02252172.

Slide credit: clinicaloptions.com

ALCYONE: Open-Label Phase III Study Design



- Primary endpoint: PFS
- Secondary endpoints: ORR, ≥ VGPR, ≥ CR, MRD (NGS at 10^{-5}), OS, safety
- Statistical analysis: prespecified interim analysis for OS with 209 events (63% of planned events)

Mateos. Lancet. 2020;395:132.

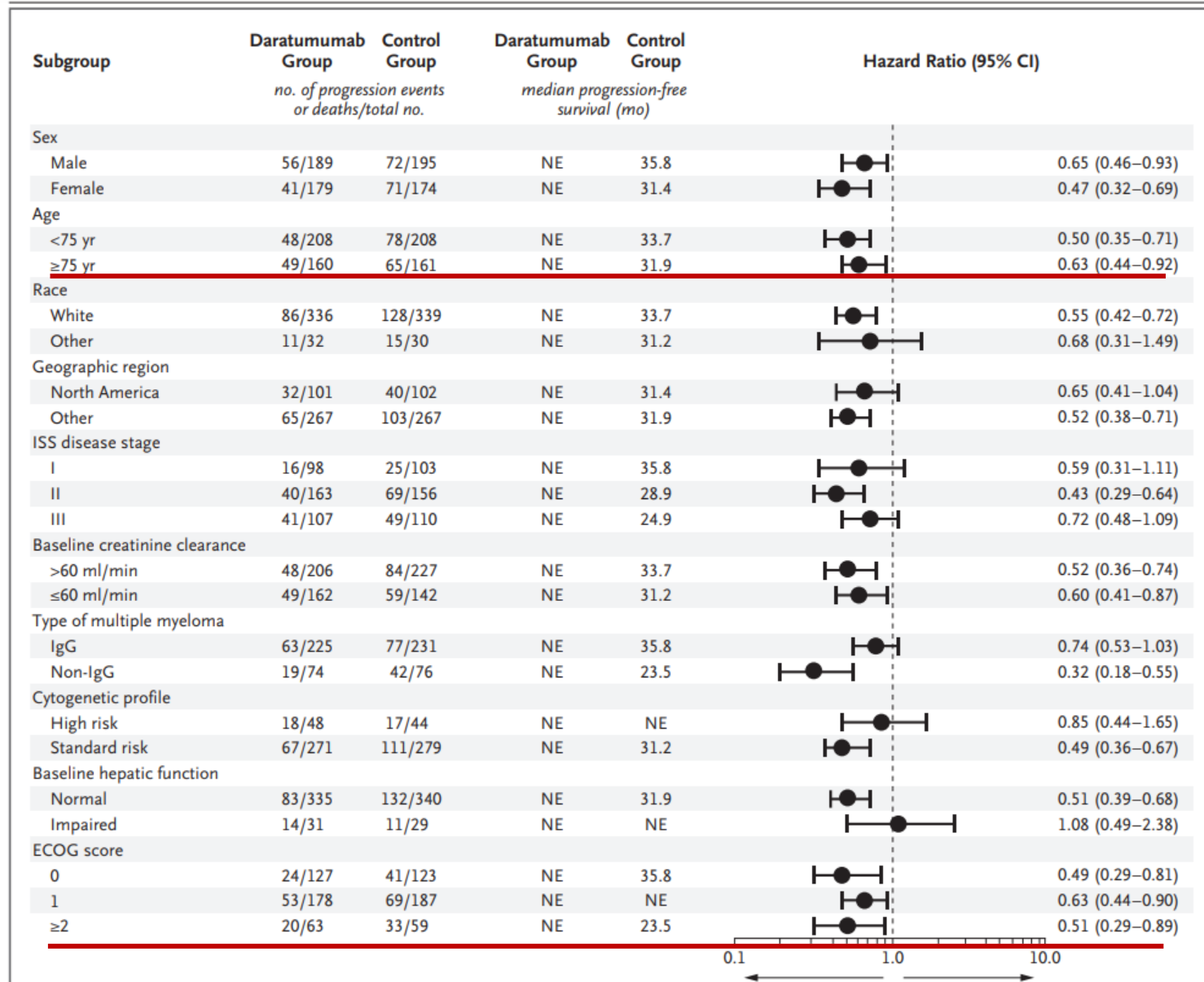
Slide credit: clinicaloptions.com

DRd vs Rd: adverse events

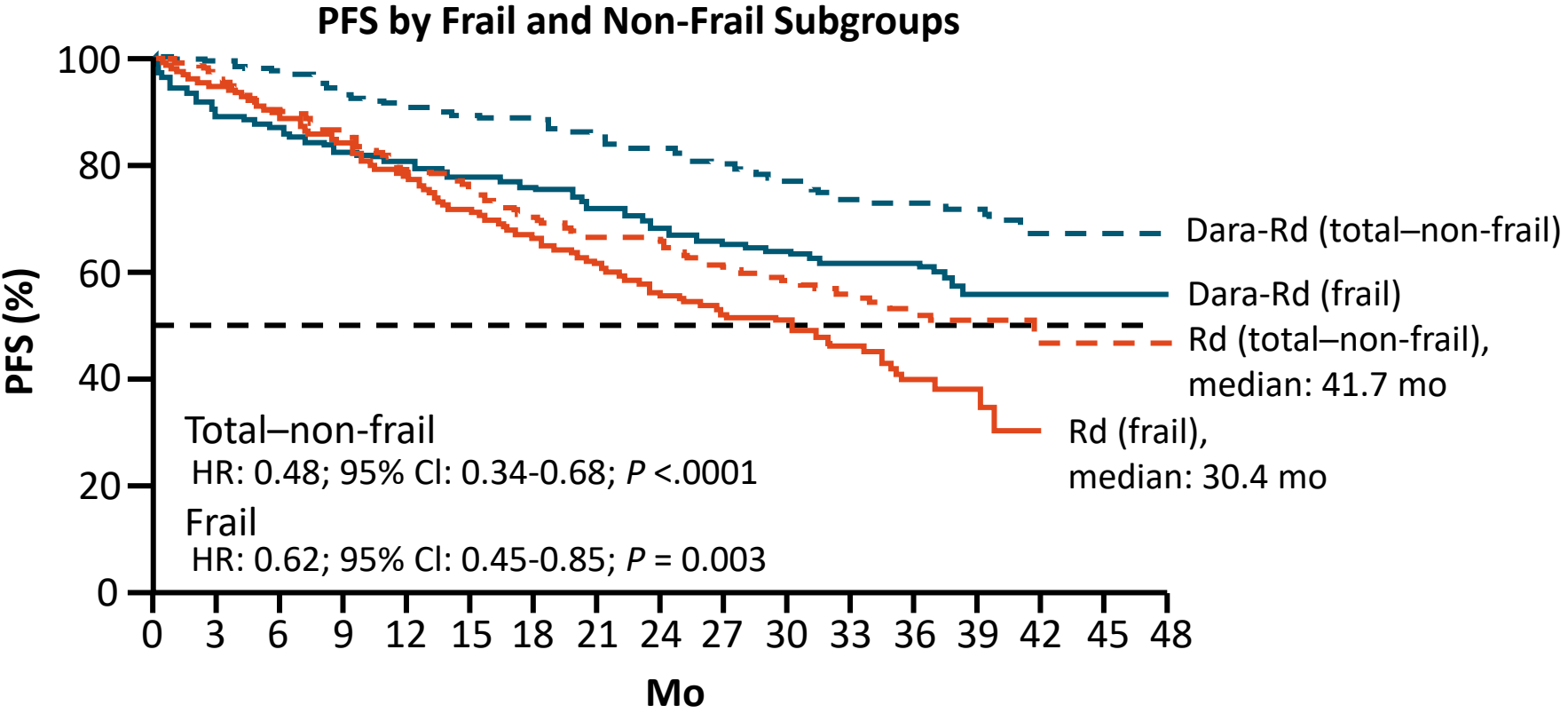
	D-Rd (n = 364)		Rd (n = 365)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hematologic, n (%)				
Neutropenia	207 (57)	182 (50)	154 (42)	129 (35)
Anemia	126 (35)	43 (12)	138 (38)	72 (20)
Thrombocytopenia	68 (19)	27 (7)	69 (19)	32 (9)
Lymphopenia	66 (18)	55 (15)	45 (12)	39 (11)
Nonhematologic, n (%)				
Diarrhea	207 (57)	24 (7)	168 (46)	15 (4)
Constipation	149 (41)	6 (2)	130 (36)	1 (<1)
Fatigue	147 (40)	29 (8)	104 (28)	14 (4)
Peripheral edema	140 (38)	7 (2)	107 (29)	2 (<1)
Back pain	123 (34)	11 (3)	96 (26)	11 (3)
Asthenia	117 (32)	16 (4)	90 (25)	13 (4)
Nausea	115 (32)	5 (1)	84 (23)	2 (<1)
Pneumonia	82 (23)	50 (14)	46 (13)	29 (8)
Deep vein thrombosis, pulmonary embolism, or both	43 (12)	23 (6)	49 (13)	23 (6)

- Rate of IRRs for D-Rd was 41% (grade 3/4: 3%)
- Incidence of SPMs was 3% for D-Rd and 4% for Rd
- Hematologic SPM was 0.5% in each arm
- TEAEs with outcome of death were 7% for D-Rd and 6% for Rd

MAIA subgroup analysis



MAIA: Impact of Frailty



Patients at Risk, n

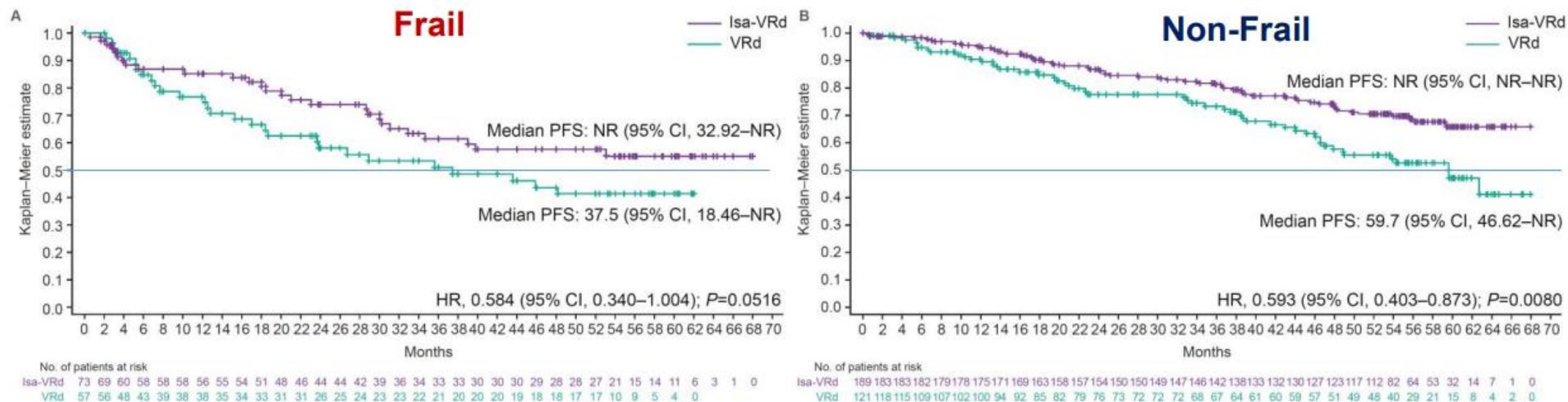
Rd (total-non-frail)	200	188	173	159	142	134	124	117	115	104	96	64	40	21	10	2	1
Dara-Rd (total-non-frail)	196	195	190	183	176	171	168	161	157	151	136	106	78	43	12	5	0
Rd (frail)	169	145	134	121	112	102	95	87	79	73	65	49	24	12	0	0	0
Dara-Rd (frail)	172	152	145	137	133	129	122	115	109	105	97	68	53	27	12	2	1

Evolving standard of care for T1E patients with NDMM: Efficacy

	MAIA ^{1,2}	IMROZ ^{3,4}	BENEFIT ^{5,6}	CEPHEUS ⁷
Induction	D-Rd vs Rd	Isa-VRd vs VRd	Isa-VRd vs Isa-Rd	Dara-VRd vs VRd
Maintenance	N/A	Isa-Rd vs Rd	Isa-VR > Isa-R vs Isa-R > Isa-R	Dara-Rd vs. Rd
N	368 vs 369	265 vs 181	135 vs 135	197 v. 198
Median follow-up	64.5 months	5 years	23.5 months	58.7 months
≥VGPR rate	81.5% vs 56.9% (P<0.001)	89.1% vs 82.9%	82% vs 70%	96% v. 94%
≥CR rate	51.1% vs 30.1% (P<0.001)	74.7% vs 64.1%	58% vs 31%	81% v. 62% (p<0.001)
MRD-negative rate (10 ⁻⁵)	32.1% vs 11.1% (P<0.001)	58.1% vs 43.6%	53% vs 26%	61% v. 40% (p<0.001)
PFS	Median: 61.9 vs 34.4 months 60-month PFS rate: 52% vs 30% (P<0.001)	5-year rate: 63% vs 45% (P<0.001)	24-month rate: 85% vs 80%	54-month rate: 68% v. 50% (p<0.001)
Age	TNE Age>65 or comorbidities	TNE Age<80	TNI- age<80 27% transplant differed	TNI- Age >65 25% transplant differed
Frailty	45% were frail Post hoc analysis	25% were frail Post hoc analysis	Frail patients included ECOG 0-2	Frail patients included ECOG 0-2

1. Facon T, et al. *New Engl J Med.* 2019;380:2104-2115. 2. Kumar SK, et al. ASH 2022. Abstract 4559. 3. Facon T, et al. ASCO 2024. Abstract 500. 4. Facon T, et al. EHA 2024. Abstract S100. 5. Leleu XP, et al. ASCO 2024. Abstract 7501.6. Leleu XP, et al. EHA 2024. Abstract S203. 7. Usmani et al *Nature Medicine* 2025

IMROZ - PFS in frail and non-frail pts



Median follow-up: 59.7 months

- **Frail:** 60-ms PFS rate: **55% vs. 41%** (HR: 0.584; 95%CI, 0.340–1.004; $P=0.052$)
- **Non-frail:** 60-ms PFS rate: **66% vs. 47%** (HR: 0.593; 95%CI, 0.403–0.873; $P=0.008$)

5y PFS in entire IMROZ group: Isa-VRd vs. VRd: 63% vs. 45% (HR: 0.6 (95%CI 0.4-0.88)

AEs =, but grade 5 AEs: 11% vs. 5.5%

Adverse Effect

	IMROZ		BENEFIT		CEPHEUS	
	IsaVRD	VRD	IsaVRD	IsaRD	DaraVRD	VRD
Neutropenia>grade 3	54%	37%	40%	45%	44.2%	29.7%
Infection> grade 3	24%	16%	35%	40%	40%	31.8%
Peripheral neuropathy	7.2%	6%	27%	10%	8.1%	8.2%

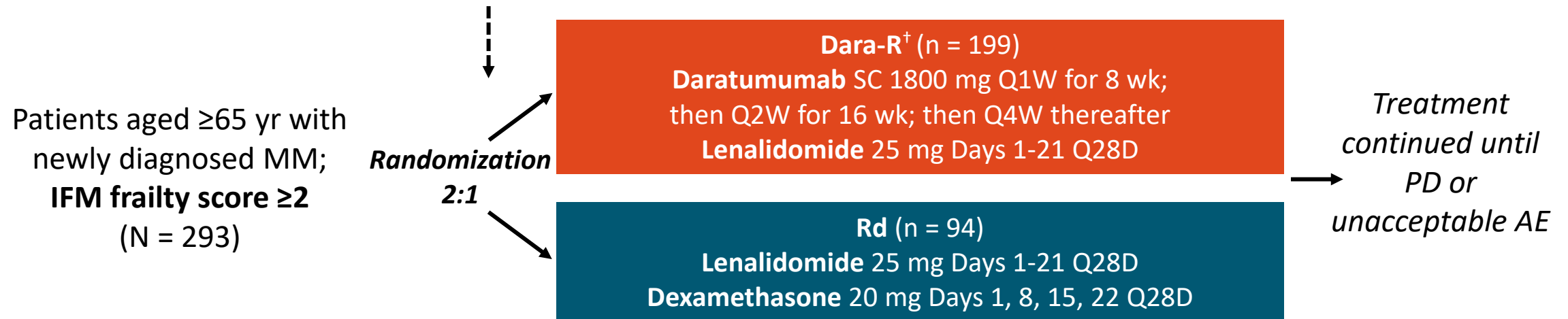
1. Facon T, et al. *New Engl J Med*. 2019;380:2104-2115. 2. Kumar SK, et al. ASH 2022. Abstract 4559. 3. Facon T, et al. ASCO 2024. Abstract 500. 4. Facon T, et al. EHA 2024. Abstract S100. 5. Leleu XP, et al. ASCO 2024. Abstract 7501.6. Leleu XP, et al. EHA 2024. Abstract S203. 7. Usmani et al Nature Medicine 2025



Frail patients

IFM 2017-03: Steroid-Sparing Regimen With Daratumumab for Patients With MM and IFM Frailty Score ≥ 2

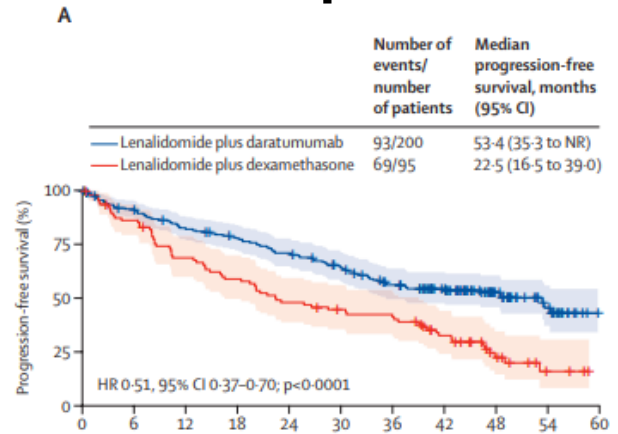
- Randomized, open-label, multicenter phase III trial¹



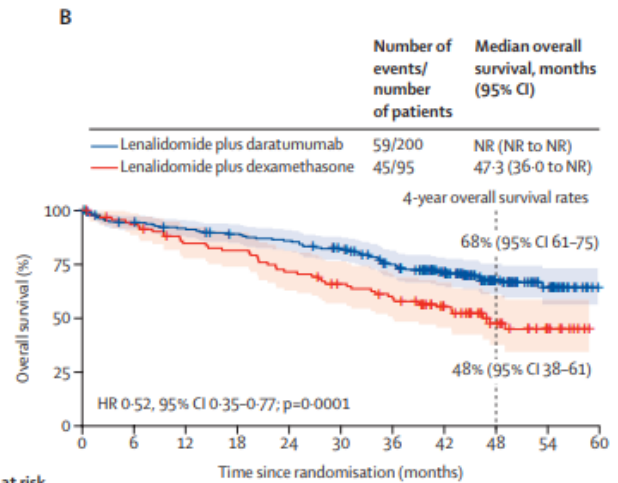
[†]DR included low-dose dexamethasone 20 mg/wk during cycles 1 and 2, along with SC daratumumab dosing.

- Primary endpoint: PFS**

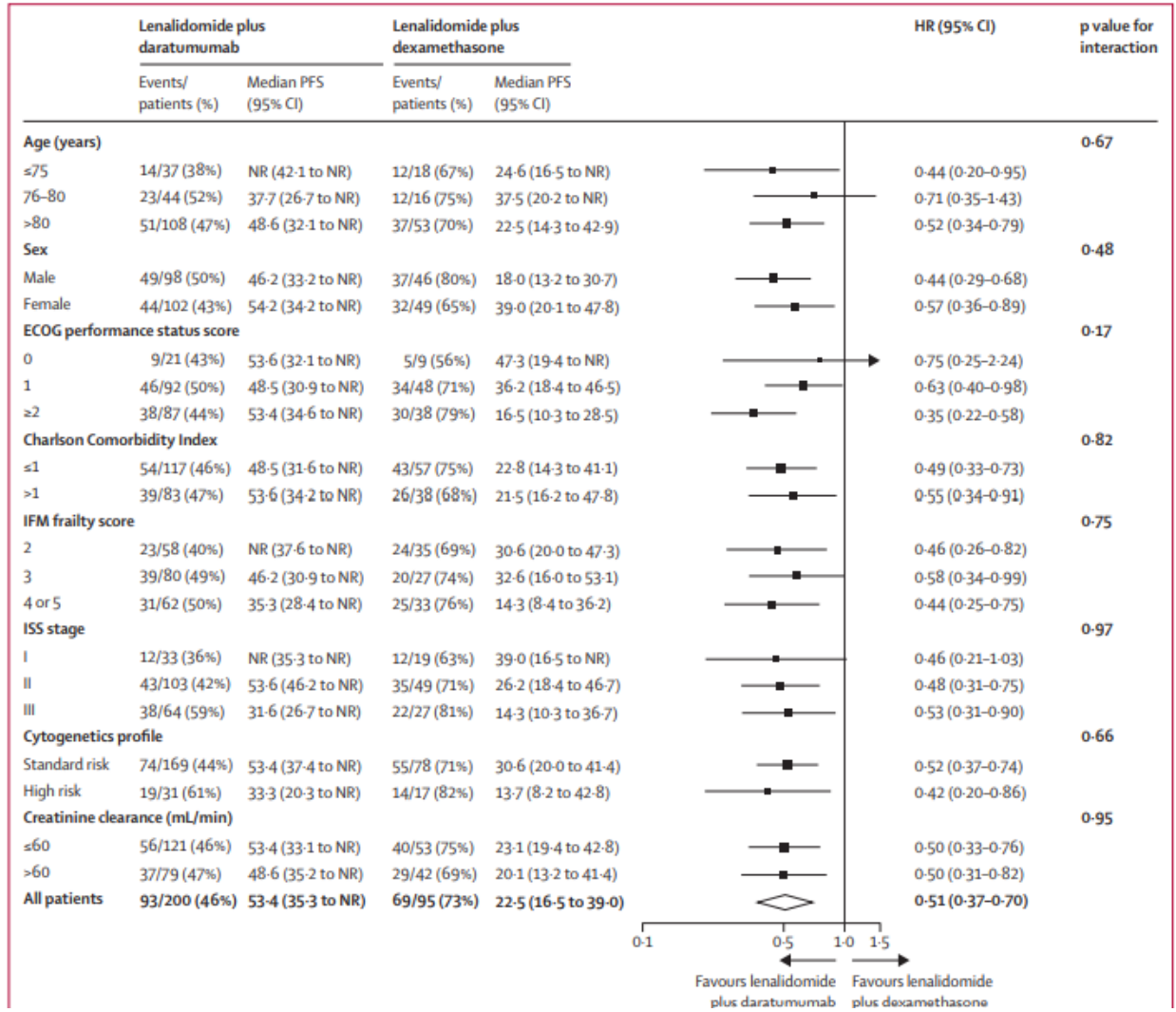
IFM 2017-03 Response rate



Number at risk (censored)	0	6	12	18	24	30	36	42	48	54	60
Lenalidomide plus daratumumab	200 (0)	178 (5)	158 (7)	147 (10)	134 (10)	117 (14)	97 (20)	79 (35)	41 (71)	20 (88)	0 (107)
Lenalidomide plus dexamethasone	95 (0)	80 (2)	63 (3)	54 (3)	44 (3)	39 (5)	36 (5)	24 (10)	11 (17)	3 (23)	0 (26)



Number at risk (censored)	0	6	12	18	24	30	36	42	48	54	60
Lenalidomide plus daratumumab	200 (0)	184 (5)	176 (7)	169 (10)	163 (10)	151 (14)	130 (23)	102 (45)	52 (91)	27 (114)	0 (141)
Lenalidomide plus dexamethasone	95 (0)	87 (2)	77 (4)	74 (4)	65 (4)	57 (7)	36 (8)	20 (19)	8 (31)	0 (42)	0 (50)

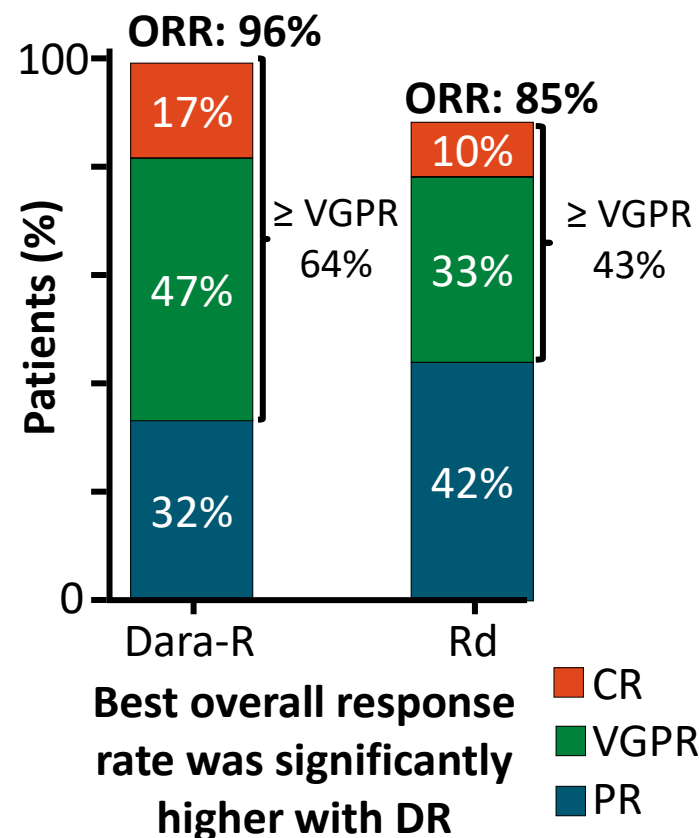


IFM 2017-03: Best Response Rate and Safety With Dara-R vs Rd

Most Common Grade ≥3 AEs, n (%)	Dara-R (n = 199)	Rd (n = 94)	P Value
All grade ≥3 AEs	164 (82)	64 (68)	.010
SAE	109 (55)	59 (63)	.21
Hematologic	109 (55)	24 (26)	<.0001
▪ Anemia	21 (11)	2 (2)	.010
▪ Neutropenia	91 (46)	17 (18)	<.0001
▪ Thrombocytopenia	18 (9)	3 (3)	.089
Infection	26 (13)	17 (18)	.29
▪ Non-COVID	17 (9)	13 (14)	.21
▪ Pneumonia	5 (3)	7 (7)	.060
▪ COVID	9 (5)	4 (4)	1
Treatment d/c for AE	27 (14)	15 (16)	.65

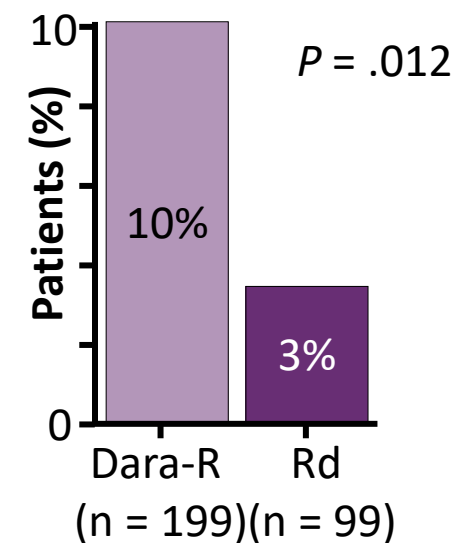
Best Response Rate and MRD

P = .001



MRD at 10⁻⁵ by NGS, in ITT analysis

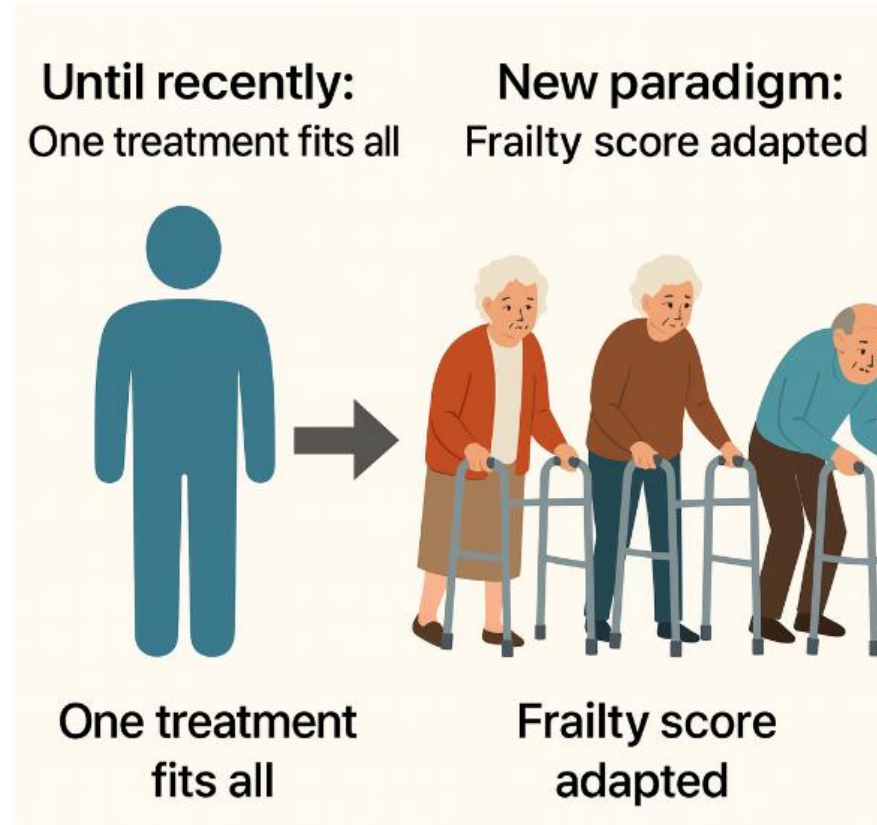
MRD assessed for patients with at least a VGPR at 12 mo. Patients with missing data were considered MRD positive



Dara-R improved rates of MRD negativity at 10⁻⁵ vs Rd

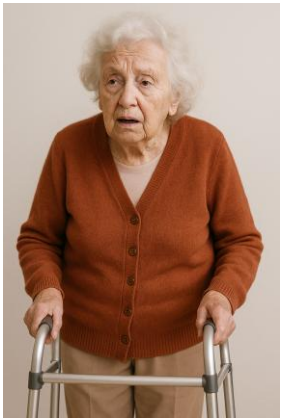
Until recently: One treatment fits all (MAYA, ALCYONE)

New paradigm: Frailty score adapted



בת 88, מתהלכת עם הליכון, ירידה קוגניטיבית לאחרונה. מושתלת קוצב בשל SSS אוסטאופורוזיס, אחרי החלפת מפרק ירך. דלקות שתן חזרות. אבחנה של מיאלומה עם איס"פ כליות ונגעים ליטיים

IgA kappa
50% תאי פלסמה
ISS 2, FISH t(4:14)
RISS 3
ECOG 2
Frailty index 2

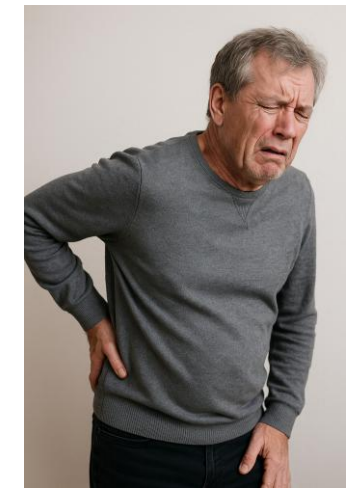


מה הטיפול המומלץ?

Level of care
האם יש סביבה תומכת, יכולה להגיע לבית החולים?
DRD-אפשר להוריד DEX אחרי 2 מחזורים
?RD

הצגת מקרים

בן 69, ברקע IHD (תפקוד לבבי תקין), סכרת מאוזנת
כאבי גב ב 4 חודשים אחרונים- אבחנה של מיאלומה עם נגעים ליטיים, סימני Spinal cord compression. ללא מחלה אקסטרמדולארית.
Free lambda myeloma, 80% תאי פלסמה
ISS 3 עם 7200 b2 microglobulin
ב FISH יש t(4,14), 17p del, RISS 3
כרגע ECOG 2- רב הזמן בכסא, מעברים Frailty index >2

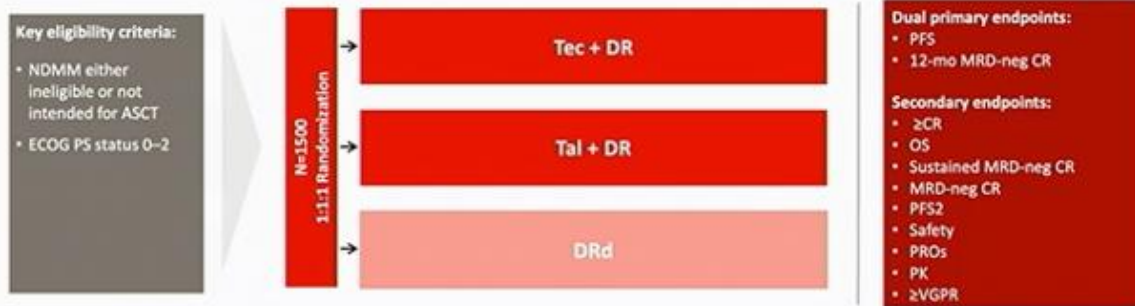


מה הטיפול המומלץ?

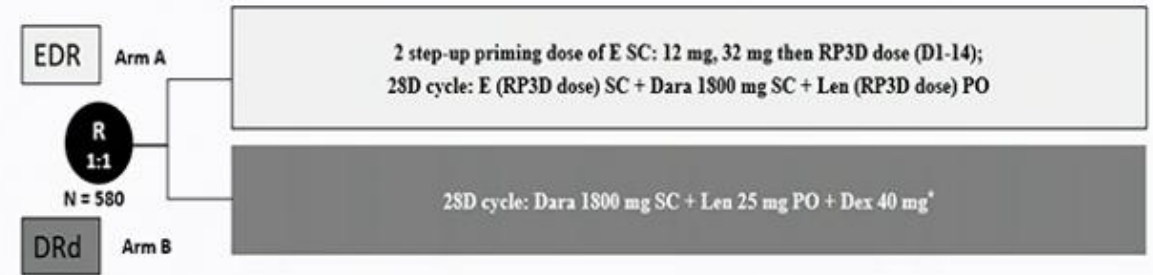
Dara Len Dex
Dara VRD
השתלה אם משתפר?

Future directions: frontline immunotherapies

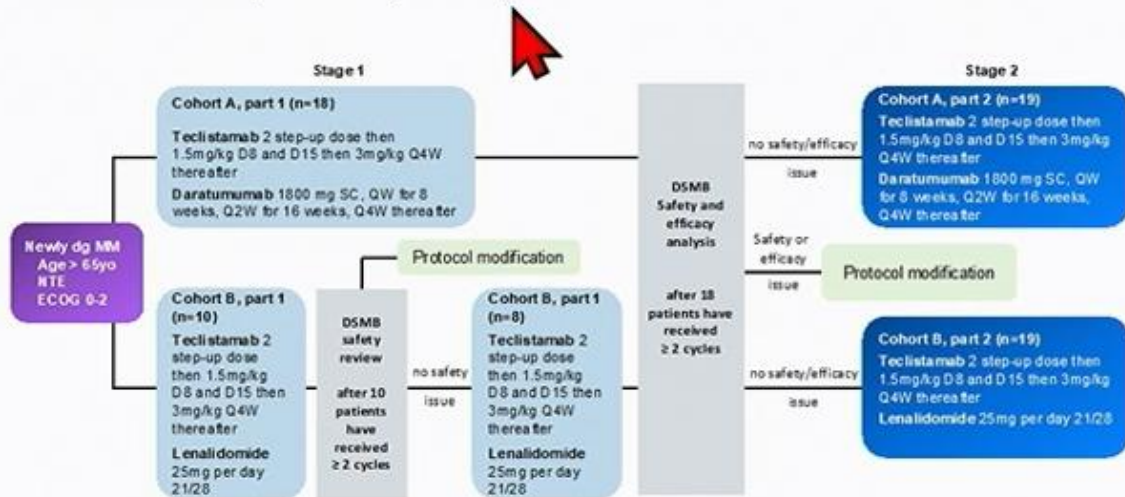
MAJESTEC-7: phase 3 (n = 1500)



MAGNETISMM-6: phase 3 (n = 580)



IFM2021-01: phase 2 (n = 74)



CARTITUDE-5: phase 3 (n = 650)

