Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

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Terapia di prima linea nel paziente non candidato a trapianto: unfit e frail

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Disclosures for Alessandra Larocca, MD

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Scientific Advisory Board	Janssen-Cilag, BMS, Amgen, Takeda, Oncopeptides, GSK, Sanofi

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

All elderly are not equal

Heterogeneous population
Variety of disease- and host-related factors

Fit patients ASCT Eligible

Based on
Age
Performance status (PS)
Comorbidities
(R-MCI score, HCT-CI) and organ function

Fit patients No ASCT Eligible

Active, independent, who exercise regularly

Unfit/Intermediate

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

Frail

Help for household tasks
Dependent on other people
Partial help for their personal care

Prognostic Factors

Disease-related Factors

- R-ISS
- Chromosomal abnormalities
- Circulating Plasma Cells
- Plasma cell Leukemia
- Extramedullary disease
- Early relapse
- Response and MRD

Patient-related Factors

- Frailty
- Age
- Renal Failure
- Co-morbidities
- Organ Function

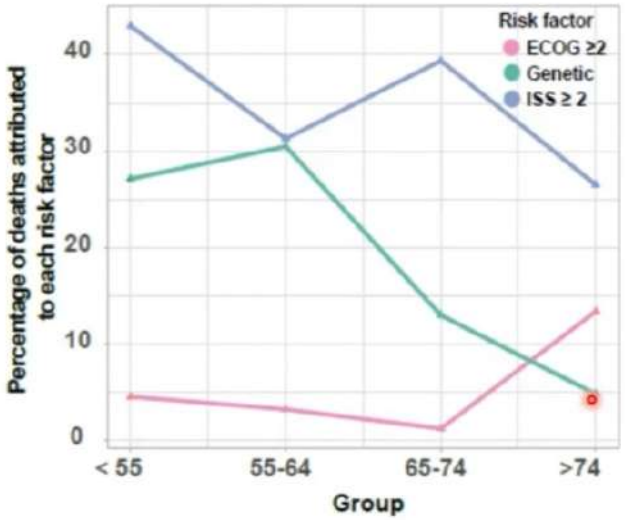
Differences in the genetic make-up of MM by age

Contribution of genetics to outcome

Event	<66 (%)	66-77 (%)	>75 (%)	p-value
del(13)	45	43.6	37	.004
t(4;14)	14.3	10.9	8.3	.001
del(17p)	6	5.9	6.1	NS

- The percentage of deaths attributed to genetics [del(1p), gain(1q), del(17p) and t(4;14)] goes down with age in favor of factors such as Performance Status and ISS

- Suggesting the contribution of conventional genetic studies to outcome in elderly patients is less important in favor of clinical features

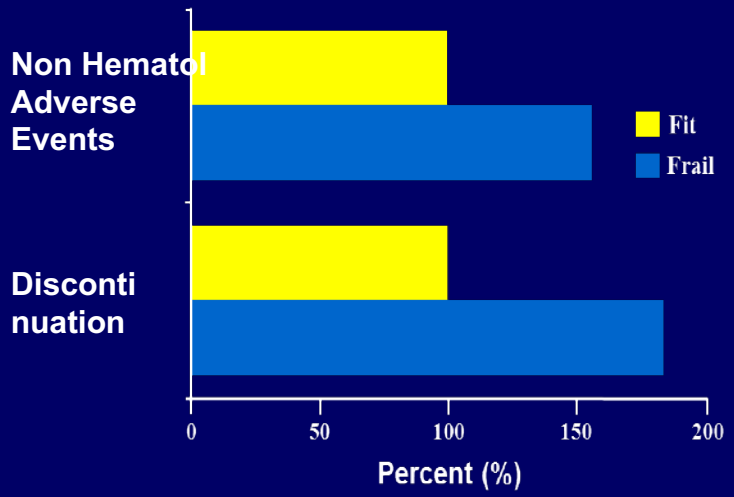


Boyle et al Leukemia *in press*

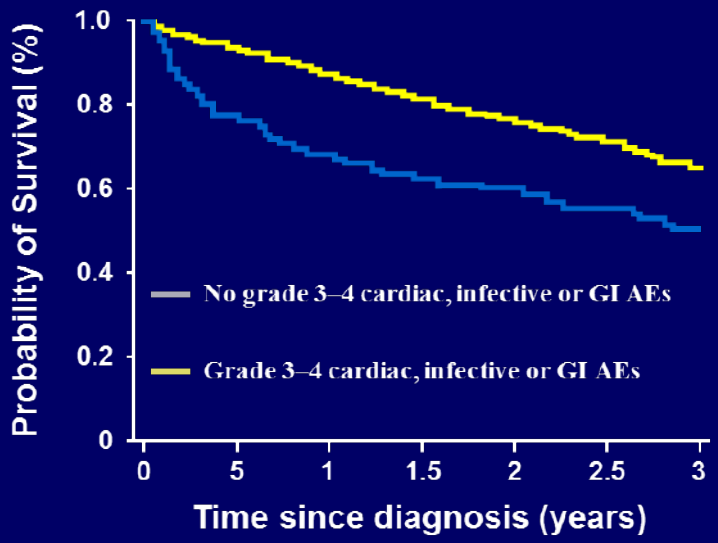
NYU Langone Health

Adverse events and toxicity

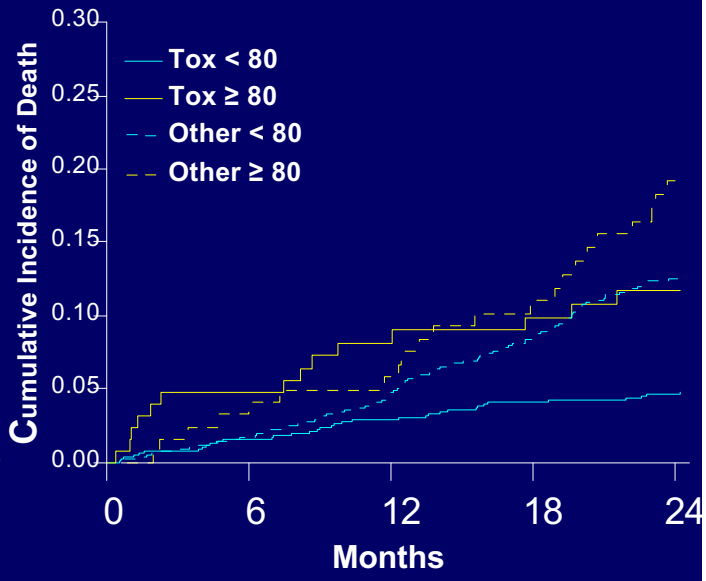
Grade 3-5 Adverse Events and Discontinuation



Overall Survival



Toxic deaths



Survival inferior due to toxic deaths

Death due to toxicity 4-fold higher and death due to other causes 2-fold higher in >80 versus <80 years

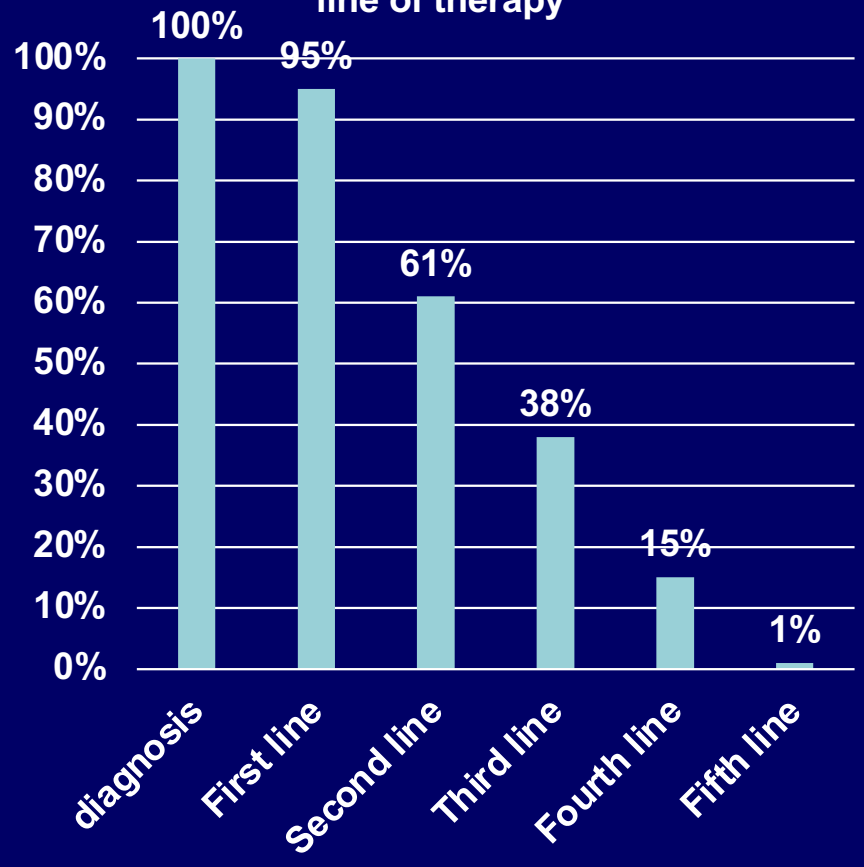
*At least one adverse event; †Due to AEs, withdrawal of consent, patient compliance, unknown; progressive disease was excluded
AE, adverse event; GI, gastrointestinal

Bringhen S, et al. Haematologica. 2013;98:980–987;
Larocca A, et al. Blood 2013;122: abstract 687
Bringhen S et al. Crit Rev Oncol Hematol 2018:130;27-35

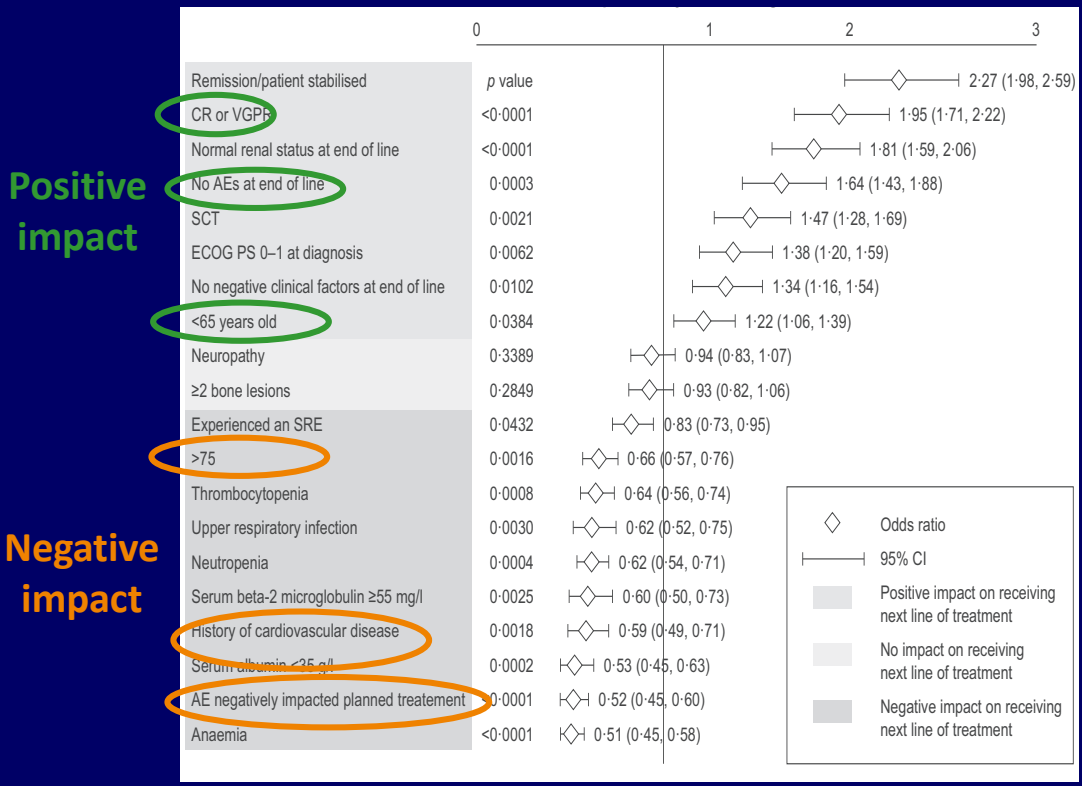
FIRST LINE TREATMENT IN ELDERLY MYELOMA PATIENTS

PROBABILITY OF RECEIVING A FURTHER LINE OF THERAPY

Proportion of patients reaching each line of therapy



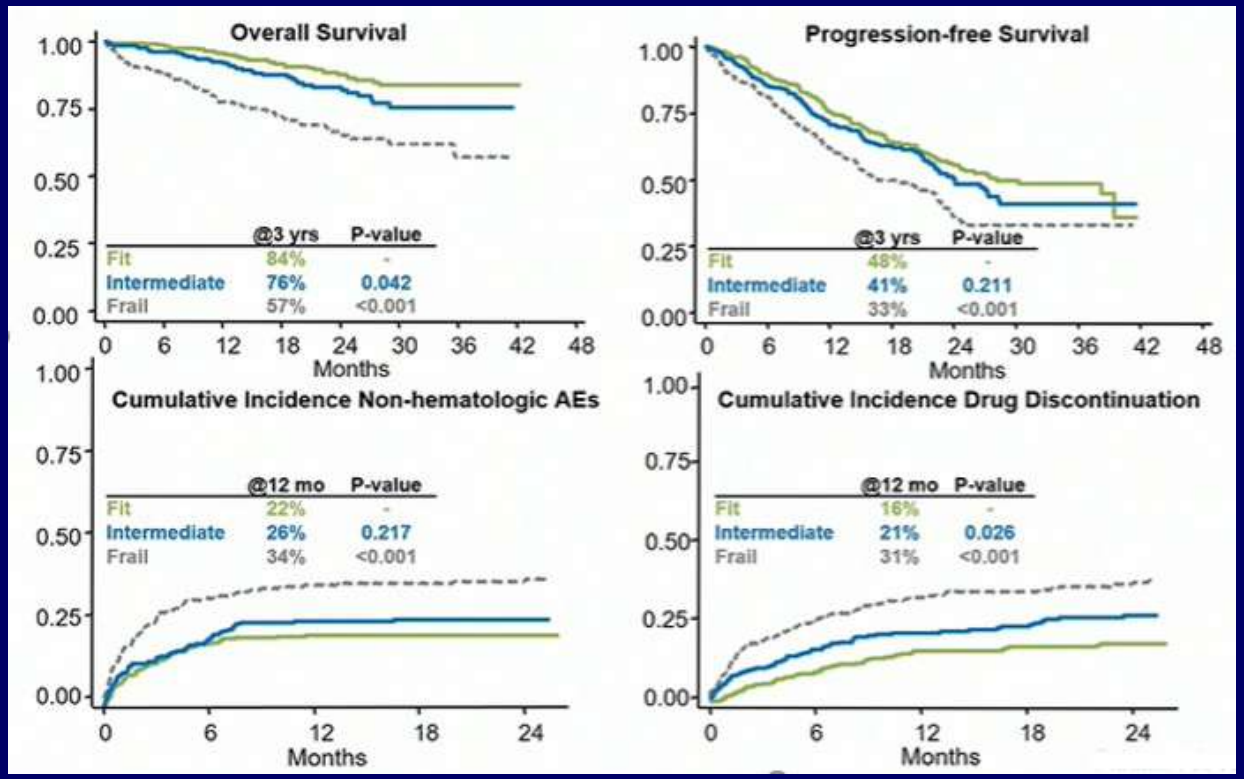
Relative probability of receiving a further line of therapy

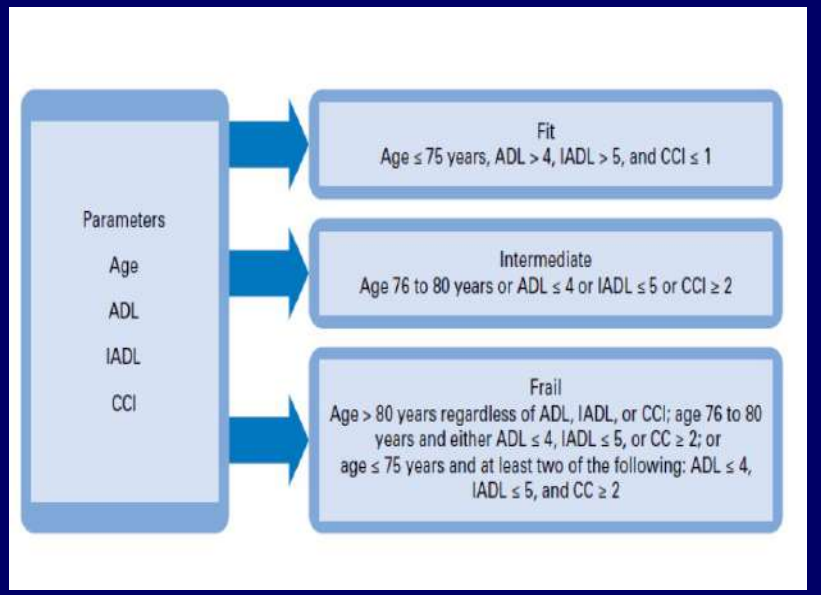


AEs, adverse events; CR, complete response; ECOG, European Cooperative Oncology Group; SCT, stem cell transplant; SRE, skeletal-related event; VGPR, very good partial response.

Yong K, et al. Br J Haematol. 2016;175(2):252-264.

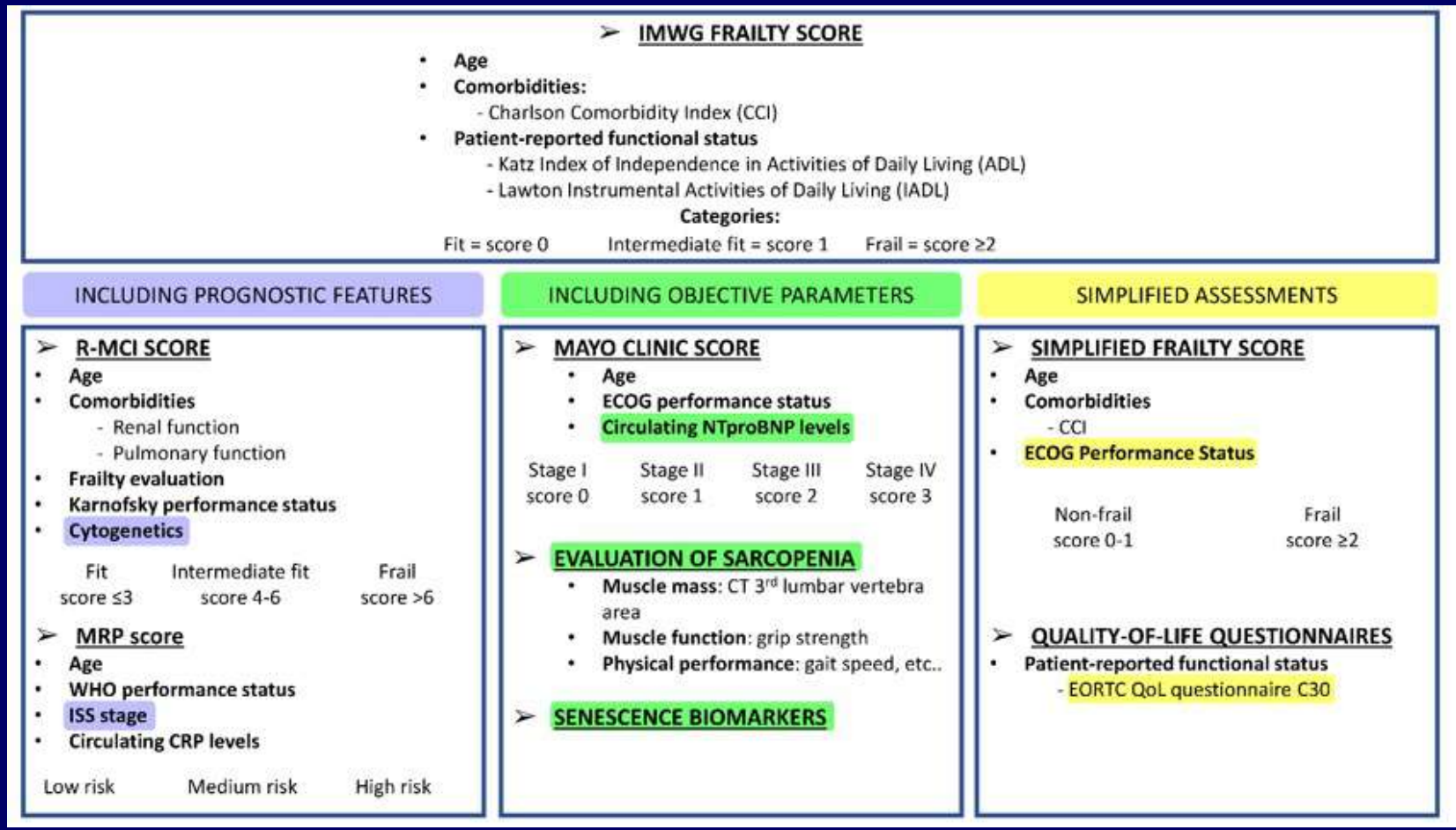
IMWG Frailty Score





Palumbo A et al. Blood. 2015; 25:2068-2074

Assessment of frailty in Myeloma

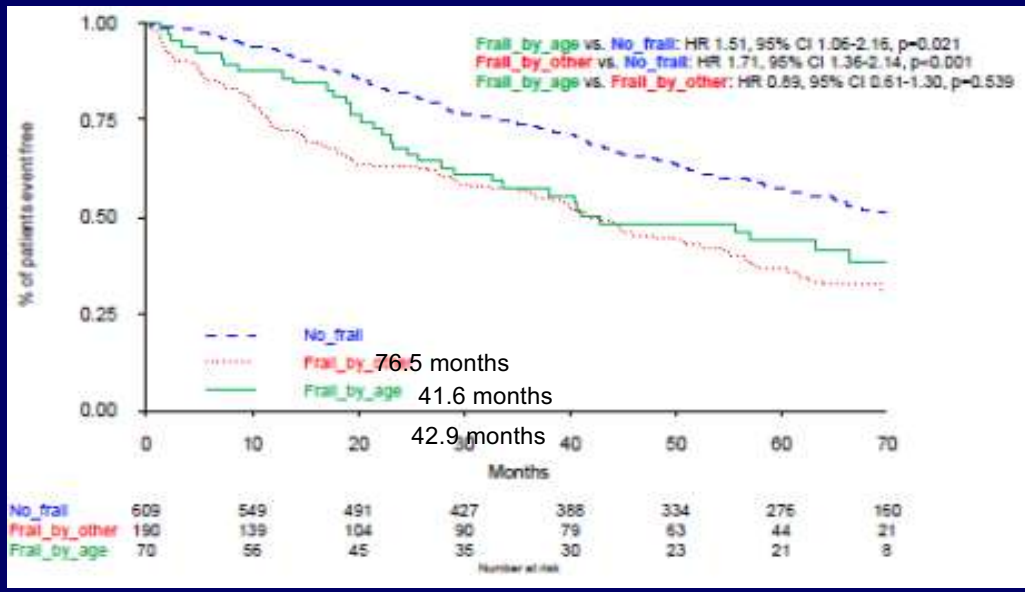


Bonello F et al. Cancers 2021, 12(11):3106

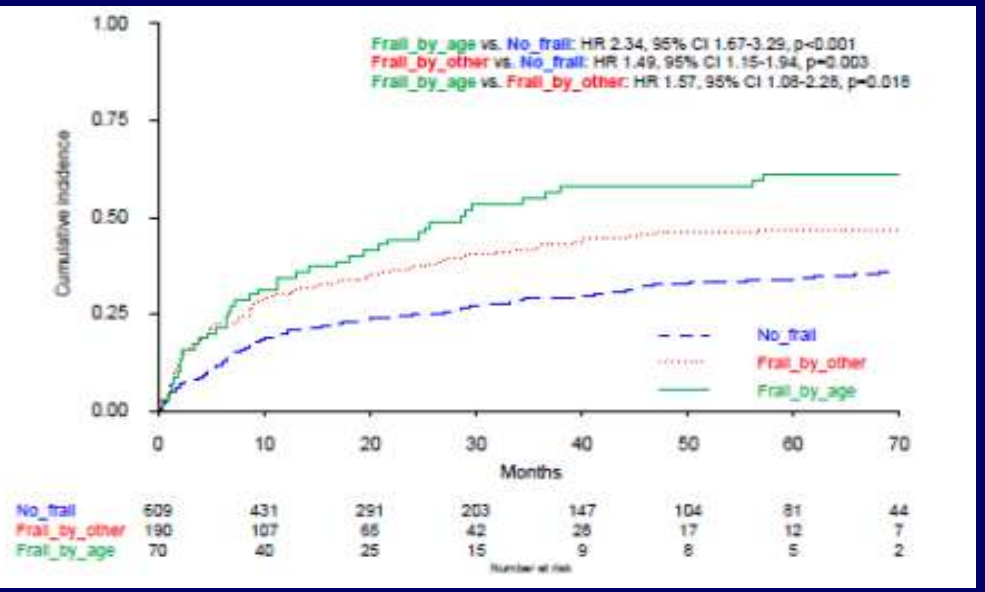
Role of chronological age > 80 ys in the IMWG Frailty Score

Frail by age only (>80 years, CCI≤1, ADL>4, IADL>5) vs. Frail_by_other

Overall Survival



Drug Discontinuation

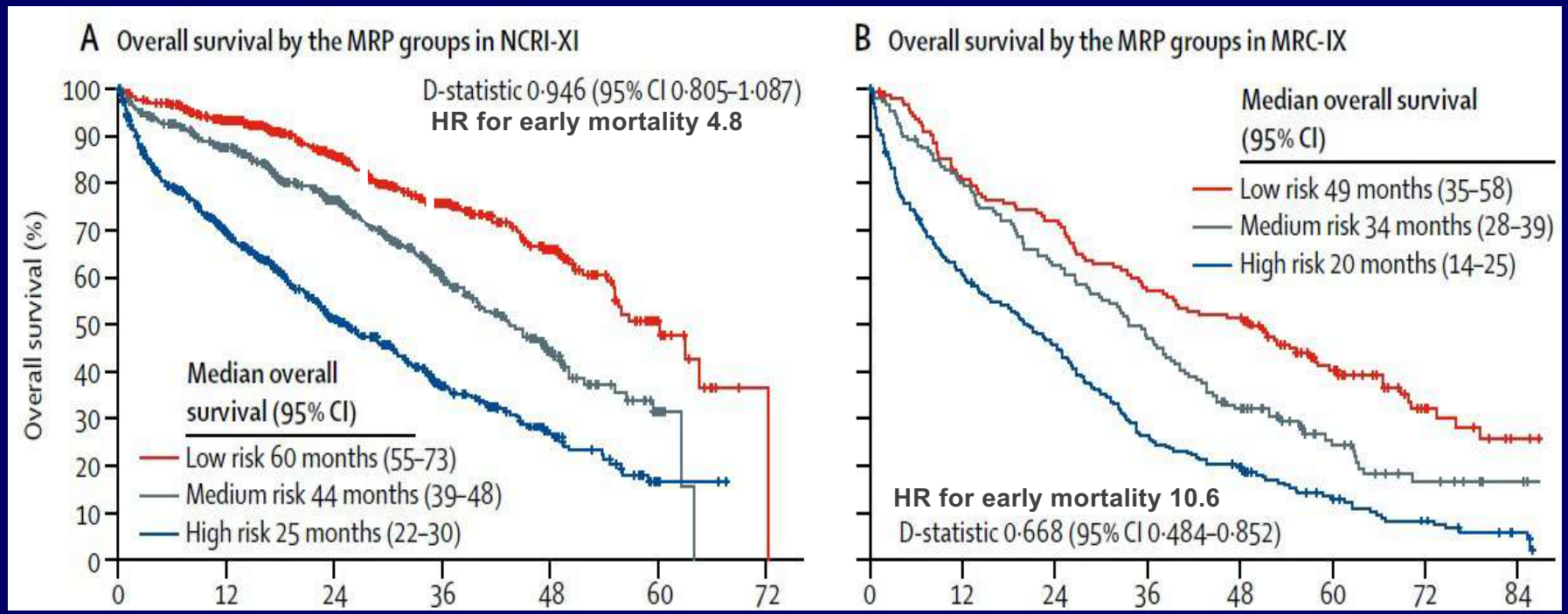


Frail by age >80 years = Frail for any other reason

D'Agostino M et al. EHA 2020.

Myeloma risk profile (MRP) is associated with outcome

Improvement by adding disease characteristics: WHO, age, ISS and CRP
Only data available in all baseline assessments, no questionnaires/scores



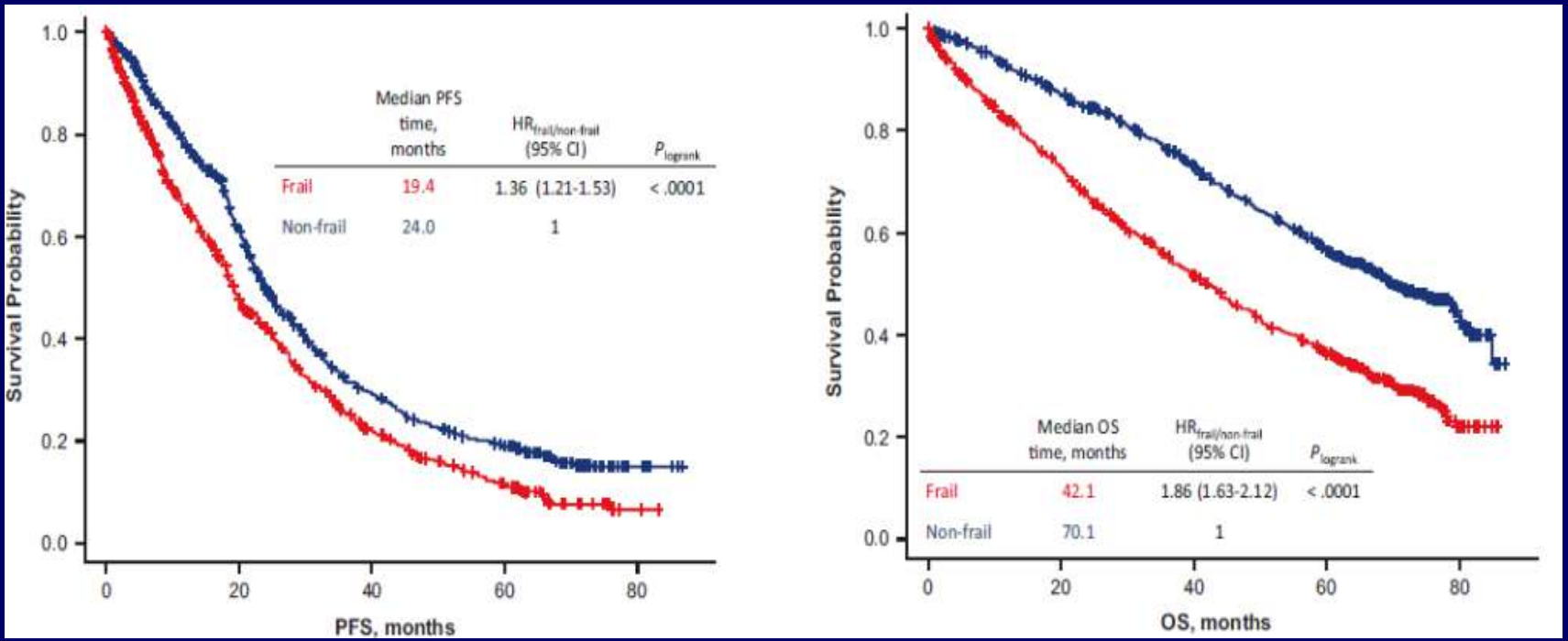
MRP, UK Myeloma Research Alliance Risk Profile; WHO, WHO performance status; ISS, International Staging System; CRP, C-reactive protein; CI, confidence interval; HR, hazard ratio; p, p-value; HR, high risk.

Cook G, et al. Lancet Haematology 2019;6(3):e154-e166
Validated: Redder et al. BJH 2020

Simplified frailty scale predicts outcomes in NDMM patients treated in the FIRST (MM-020) trial

Simplified Frailty scale assessed with age, Charlson Comorbidity Index (CCI), and ECOG PS

Retrospective analysis (n = 1618) : frail (49%) and non-frail (51%) patients



Facon T, et al. Leukemia 2020;34:224–233.

A single centre retrospective analysis on the ability to identify transplant-ineligible patients with MM who are not likely to benefit from new standard therapies

- Retrospectively simplified frailty scores, proposed by Facon et al (Leukemia 2000) based on age, ECOG PS and CCI
- 189 patients, 23% older than 80 years
- 70% were classified as frail and 30% non-frail
- CCI>1, PS ≥2 and albumin level ≤ 3g/dL whereas age was not found a factor affecting early mortality. Using albumin level ≤3 g/dL instead of age > 80, present in the Facon scale, the new score was able to stratify patients in frail (score 3-5, n= 55, 29.5%) and non-frail (score 0-2, n=155, 70.5%).
- **Conclusion:** Facon score could be improved using simple parameter as albumin level, to increase the ability to detect patients with the highest risk of early mortality

Offidani M et al Clinical Lymphoma Myeloma and Leukemia Volume 21, Supplement 2, October 2021, Page S124

COMPASS: a prospective study comparing clinical (CA) vs geriatric assessment (GA) in NDMM patients

- 200 NDMM patients ≥ 70 years, 74% of patients were ≥ 75 years
- CA performed by the treating physician; GA (G8) independently by a trained health care worker.
- 43% of patients were frail by CA; 69% had a geriatric risk profile by G8.
- Patients fit by CA but frail by G8 (fit-frail) were older (p=0,002), had reduced nutritional status (p<0,001), more recent weight loss (p<0,001), more polypharmacy (p<0,001), compared to fit by CA and G8 (fit-fit).
- CA fit but G8 frail patients were more independent on ADL, iADL, and had less cognitive impairment compared with frail patients by both CA and G8.
- Fit by CA but frail by G8 score were categorized into intermediate fit (31%) and frail (57%) by IMWG frailty score.
- After 3 months of treatment, the majority of patients remained in the same category (fit or frail) by CA and by G8 (respectively 82% and 80%), reinforcing that frailty status at diagnosis is not driven by myeloma-related symptoms.

CA underestimates the geriatric risk profile in 25% of NDMM elderly patients

Delforge M et al Clinical Lymphoma Myeloma and Leukemia Volume 21, Supplement 2, October 2021, Page S124

Experimental trial *versus* real-life population

Are patients in clinical trial really frail?

	SWOG S0777	ALCYONE	MAIA
Median age (years) ≥ 75 years >80 years	63 65 43% Not reported	71 30% Not reported	73 44% Not reported
ECOG PS 0-1 2 > 2	 86% 14% 2-3 Excluded >3	 75% 25% Excluded	 83% 17% Excluded
Creatinine clearance 30-60 ml/min < 30 ml/min	 5% creatinine > 2mg/dL excluded	 41% excluded (< 40 ml/min)	 41% excluded
Exclusion criteria	Previous malignancy NYHA III/IV Recent myocardial infarction	AST/ALT > 2.5 ULN Malignancy < 3 years Myocardial infarction < 1 year	AST/ALT > 2.5 ULN Malignancy < 5 years Myocardial infarction < 1 year

Durie B et al, Blood 2018; 132;1992; Durie et al; Blood Cancer J; 10:53; Mateos MV et al, Lancet 2020; 395(10218):132-141; Facon T et al, N Eng J Med 2019 380, 2105-15

Experimental trial *versus* real-life population

Clinical trial Efficacy	*Real life* Effectiveness
Limited number of patients	All patients
Selected patients	Not selected patients
Restrictive inclusion criteria	Logistics (lack of care-giver, distance from site)
Limited comorbidities	Several/Some comorbidities
Intensive monitoring of patients	Not always appropriate compliance
Enrolled in clinical trial units	Cummunity-based setting
Lack of frailty-tailored endpoint (i.e. quality of life)	Tailored treatment at physician judgment

Management of frail and intermediate (unfit) MM patients

Phase III trials in NDMM not eligible for ASCT

VMP
VMP vs MP: PFS: **24** vs 16m (▲8m **)** OS: **56** vs 43m. (▲13 m)

Rd
Rd vs Rd18 vs MPT PFS: **26** vs 21m. (▲5m) OS: **59** vs 49m (▲10 m)

	SWOG (N = 484) VRd vs Rd[1]	TOURMALINE (N = 705) IRd vs Rd[3]	ENDURANCE (N = 1087) KRd vs VRd[2]	ALCYONE (N = 706) DVMP vs VMP[4]	MAIA (N = 737) DRd vs Rd[5]
PFS (mos) (▲mos)	**34** vs 24 ▲ 10	**35** vs 22 ▲ 13.5	**34** vs 34 =	**36** vs 19 ▲ 17	**60+** vs 34 ▲ 26+
OS	**65 mos**	**NA**	**84%@3y**	**78% vs 68%@3y**	**66% vs 53%@ 5y**

ASCT, autologous stem cell transplant; d, dexamethasone; D, daratumumab; K, carfilzomib; M, melphalan; NA, not assessed; P, prednisone; R, lenalidomide; V, bortezomib

1. Durie B et al. Lancet 2017;389:519; 2. Kumar S et al. ASCO 2020; abstract LBA3;
3. Facon T et al. Blood 2021;. 4. Mateos. Lancet 2019; 395:132-41
5. Facon T. N Eng J Med 2019;380:2104 and Lancet Oncol 2021 in press.

Courtesy by Facon T IMW 2021

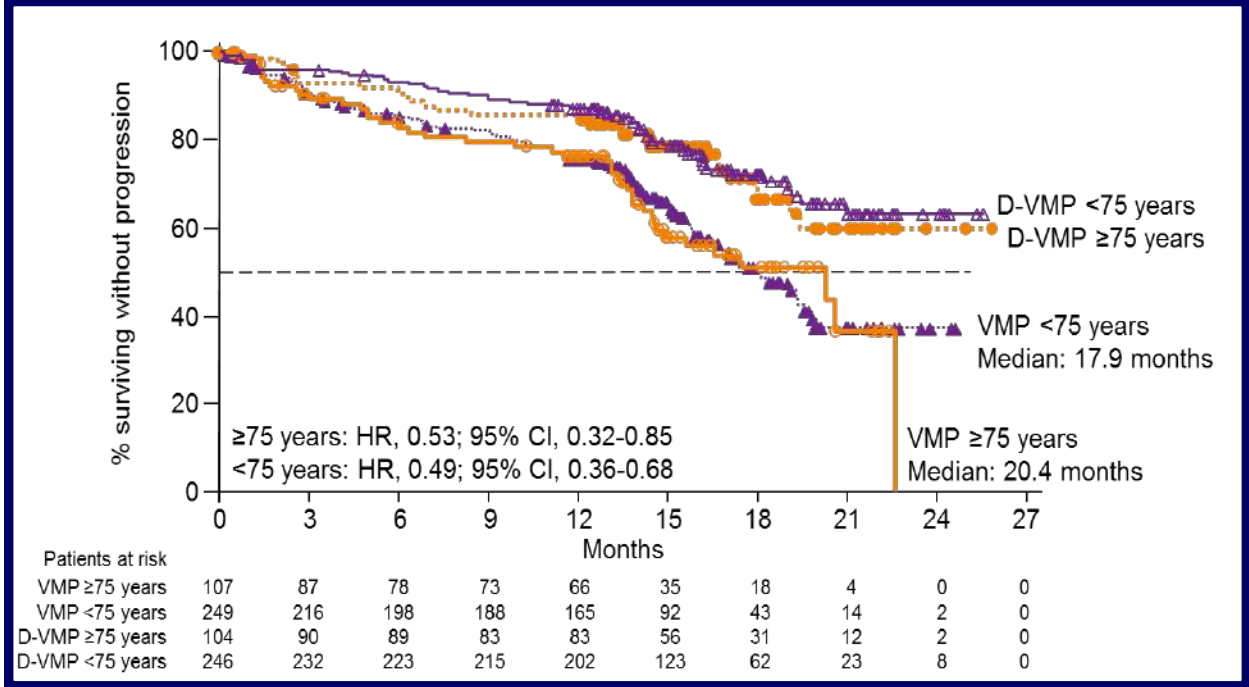
Daratumumab in first line

Impact of age on outcomes

ALCYONE study: D-VMP > VMP

Median age 71 years (range 40-93)

≥75 years 29.7%



MAIA study: D-Rd > Rd

Median age 73 years (range 45-90)

≥75 years 43.5%

	Rd		D-Rd		HR (95% CI)
	n/N	Median	n/N	Median	
Sex					
Male	90/195	32.3	67/189	NE	0.61 (0.44-0.83)
Female	81/174	34.4	53/179	NE	0.50 (0.35-0.70)
Age					
<75 years	91/208	35.4	58/208	NE	0.49 (0.35-0.69)
≥75 years	80/161	31.9	62/160	NE	0.62 (0.44-0.87)
Race					
White	152/339	34.4	108/336	NE	0.56 (0.44-0.71)
Other	19/30	30.4	12/32	NE	0.54 (0.26-1.11)
Region					
North America	51/102	30.4	36/101	NE	0.53 (0.35-0.82)
Other	120/267	35.1	84/267	NE	0.56 (0.42-0.74)
Baseline renal function (CrCl)					
>60 mL/min	98/227	37.1	62/206	NE	0.54 (0.40-0.75)
≤60 mL/min	73/142	29.7	58/162	NE	0.55 (0.39-0.77)
Baseline hepatic function					
Normal	158/340	33.7	105/335	NE	0.52 (0.40-0.66)
Impaired	13/29	34.5	15/31	29.2	0.97 (0.46-2.05)
ISS staging					
I	29/103	NE	21/98	NE	0.61 (0.35-1.08)
II	82/156	29.7	55/163	NE	0.48 (0.34-0.67)
III	60/110	24.2	44/107	NE	0.61 (0.41-0.89)

In both studies, no impact of age was observed

CI, confidence interval; D, daratumumab; HR, hazard ratio; PFS, progression-free survival; VMP, bortezomib-melphalan-prednisone.

Mateos MV et al. N Engl J Med 2018;378:518-28

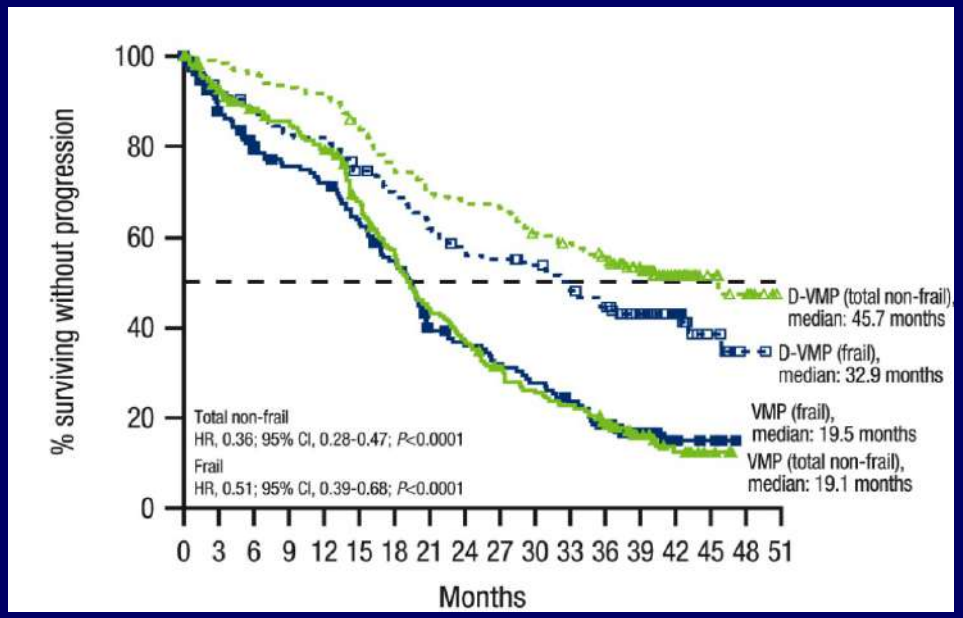
Usmani SZ, et al., ASCO 2019; abstract 8035, oral presentation

Daratumumab in first line

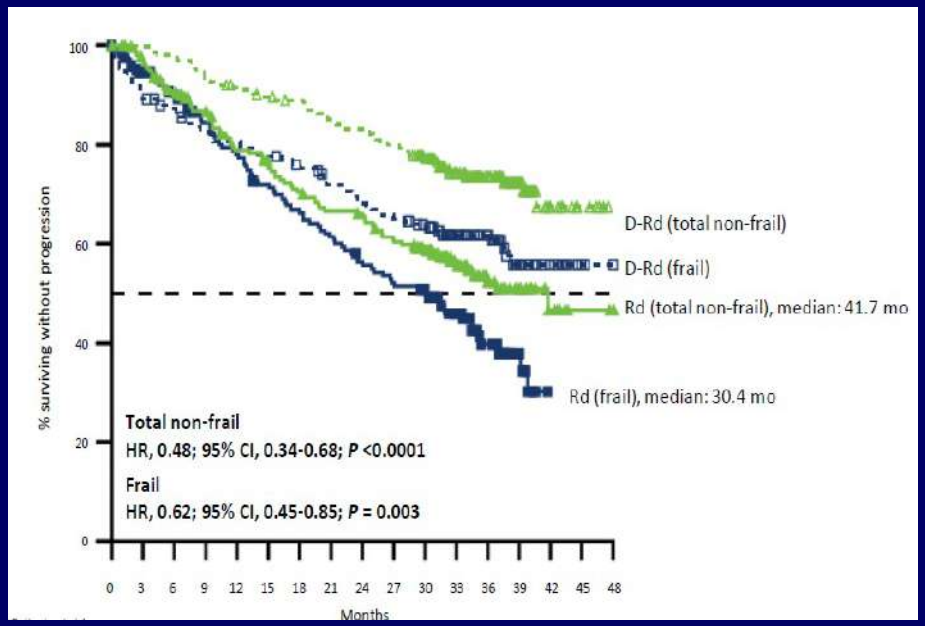
Impact of frailty on outcomes

PFS in the total non-frail and frail subgroups

ALCYONE



MAIA



Non-frail patients had longer PFS than frail patients, but the PFS benefit of the addition of Dara was maintained across frailty subgroups

Mateos MV, et al. Clin Lymphoma Myeloma Leuk. 2021, epub ahead of print; Zweegmann et al, EMN 2021. Facon T et al. Leukemia 2022

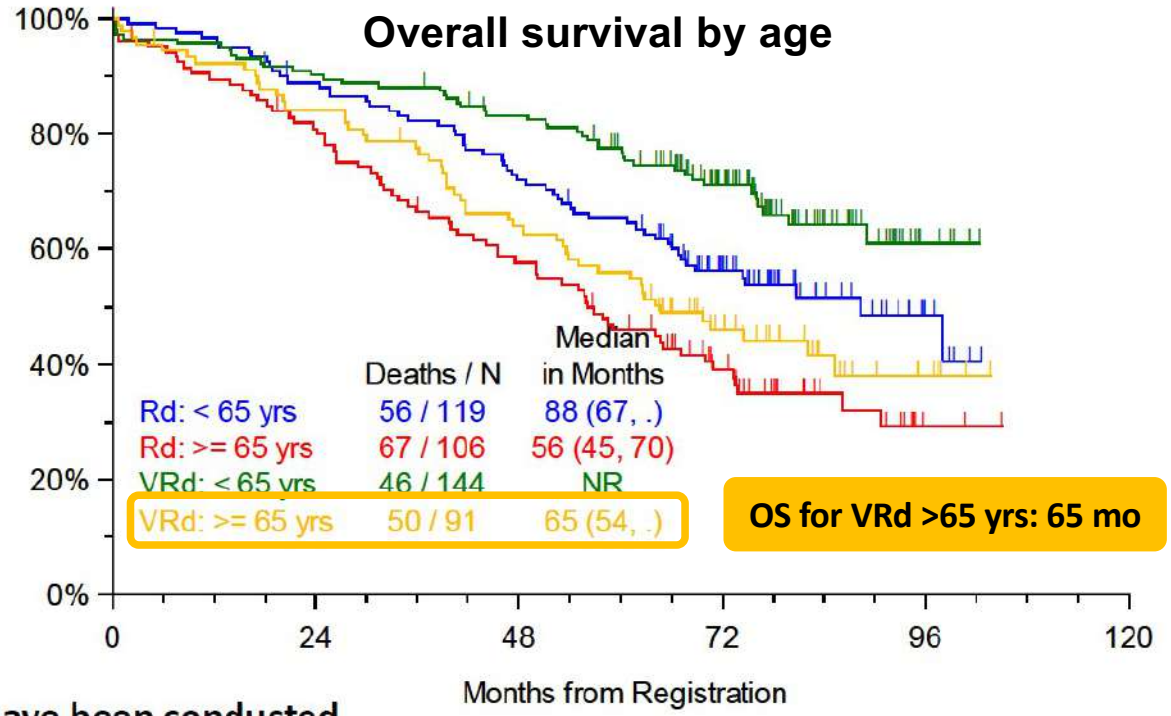
VRd-Rd vs continuous Rd: SWOG SO777 trial

Impact of age on outcomes

Age ≥65 years 43% overall, VRd 38%

Median PFS (months)

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



*For all analyses, both SWOG and IRC assessments have been conducted using the fully updated datasets with current datalock in May 2018

VRd improved outcome compared with Rd, irrespective of age

Durie B et al. ASH 2018, abstract 1992, poster presentation; Durie B et al BCJ 2020

V, bortezomib; R, lenalidomide; d, dexamethasone; PFS, progression-free survival; OS, overall survival; p, p-value; yrs, years, mo, months.

Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up

Meletios A. Dimopoulos[1], Philippe Moreau[2], Evangelos Terpos[1], María-Victoria Mateos[3], Sonja Zweegman[4], Gordon Cook[5], Michel Delforge[6], Roman Hájek[7], Fredrik Schjesvold[8,9], Michele Cavo[10], Hartmut Goldschmidt[11], Thierry Facon[12], Hermann Einsele[13], Mario Boccadoro[14], Jesús San-Miguel[15], Pieter Sonneveld[16], Ulrich Mey[17], on behalf of the EHA Guidelines Committee and the ESMO Guidelines Committee

Patient-frailty index and frailty index-defined risk factor assessment via IMWG-FI and Revised Myeloma Comorbidity Index

Patient risk factors
Age >75 years
Mild, moderately, or severely frail (patients who need help with either household tasks, personal care, or are completely dependent)
Comorbidities (pulmonary, renal, cardiac and hepatic dysfunction) And/or Preferably with (a) IMWG-frailty index[1] and/or (b) R-MCI[2] define fit, intermediate-fit, and frail patients, in order to consider adapting antimyeloma therapy; fit level 0, intermediate fit level 1 and frail level 2.

http://www.myelomafrailtyscorecalculator.net
http://www.myelomacomorbidityindex.org/

Dimopouolos MA et al. Annals of Oncology 2021

Treatment adjustment based on patient frailty/fitness

EHA-ESMO Guidelines

Frailty index risk factors				
IMWG frailty index[1]	0	1	1 + occurrence of grade 3-4 haematological AE	≥2
R-MCI[2]	1-3	4-6	7-9	
Dose level	0	1	-2	-2
Treatment doses	**Level 0**	**Level 1**	**Level 2**	
Prednisone	2 mg/kg days 1-4 of a 4-6-week cycle 60 mg/m^2 days 1-4 of a 6-week cycle	1 mg/kg days 1-4 of a 4-6-week cycle 30 mg/m^2 days 1-4 of a 6-week cycle	0.3-0.5 mg/kg days 1-4 of a 4-6-week cycle 10-15 mg/m^2 days 1-4 of a 6-week cycle	
Dexamethasone	40 mg day 1, 8, 15, 22 of a 28-day cycle	20 mg day 1, 8, 15, 22 of a 28-day cycle	10 mg day 1, 8, 15, 22 of a 28-day cycle	
Melphalan	0.25 mg/kg days 1-4 of a 4-6 week cycle 9 mg/ m^2 days 1-4 of a 6-week cycle	0.18 mg/kg days 1-4 of a 4-6 week cycle 7.5 mg/m^2 days 1-4 of a 6-week cycle	0.13 mg/kg days 1-4 of a 4-6-week cycle 5 mg/ m^2 days 1-4 of a 6-week cycle	
Thalidomide	100 (-200) mg/day	50 (-100) mg/day	50 mg qod (- 50 mg/day)	
Lenalidomide	25 mg days 1-21 of a 28-day cycle	15 mg days 1-21 of a 28-day cycle	10 mg days 1-21 of a 28-day cycle	
Pomalidomide	4 mg days 1-21 of a 28-day cycle	3 mg days 1-21 of a 28-day cycle	2 mg days 1-21 of a 28-day cycle	
Bortezomib	1.3 mg/m^2 twice weekly	1.3 mg/m^2 once weekly	1.0 mg/m^2 once weekly	

	Day 1, 4, 8, 11 every 3 weeks	Day 1, 8, 15, 22 every 5 weeks	Day 1, 8, 15, 22 every 5 weeks
Carfilzomib[a]	20 mg/m^2 day 1, 2, 8, 9, 15, 16 cycle 1, 27 mg/m^2 cycle 2 every 3 weeks	20 mg/m^2 cycle 1 → 27 mg/m^2 cycle 2, day 1, 8, 15, every 3 weeks	20 mg/m^2 day 1, 8, 15, every 4 (5) weeks
Ixazomib	4 mg day 1, 8, 15, every 4 weeks	3 mg day 1, 8, 15, every 4 weeks	2.3 mg day 1, 8, 15, every 4 weeks
Daratumumab[a]	16 mg/kg bw, cycle 1-8: weekly; cycle 9-24: day 1+15, from week 25: every 4 weeks	16 mg/kg bw, cycle 1-8: weekly; cycle 9-24: day 1þ15, from week 25: every 4 weeks	16 mg/kg bw,cycle 1-8: weekly; cycle 9-24: day 1+15, from week 25: every 4 weeks
Elotuzumab[b]	10 mg/kg bw, day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15	10 mg/kg bw, day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15	10 mg/kg bw, day 1, 8, 15, 22 cycle 1þ2, from cycle 3: day 1þ15
Panobinostat	20 mg day 1, 3, 5, 8, 10, 12 every 4 weeks	15 mg day 1, 3, 5, 8, 10, 12 every 4 weeks	10 mg day 1, 3, 5, 8, 10, 12 every 5 weeks

Expert-opinion dose modification guidelines are available to adapt treatment

Dimopouolos MA et al. Annals of Oncology 2021

Dose-adapted treatment
Modified VRd (VRd-lite)

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.

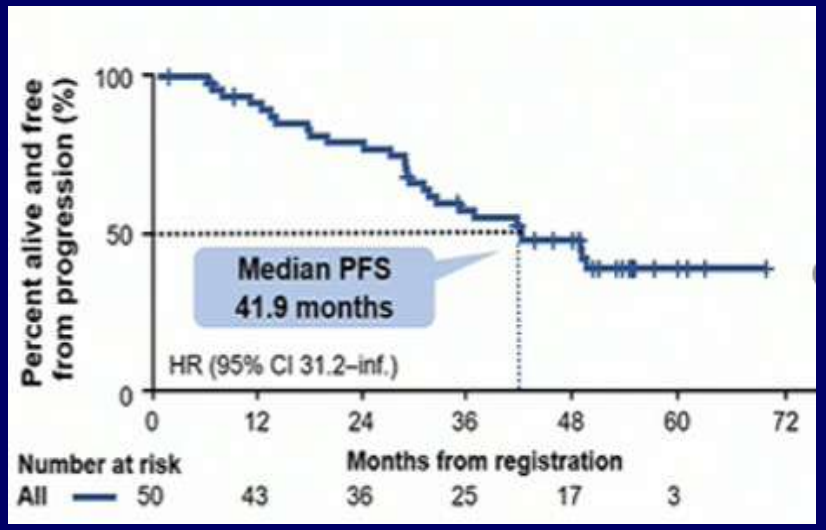
Phase 2 Study

Median age 73 years

ORR 86%, ≥VGPR 66%, ≥CR 44%

Any grade PN 60%, Grade 3-4 PN 2%

Grade 3-4 AEs: Fatigue 16%, Rash 10%, Neutropenia 14%

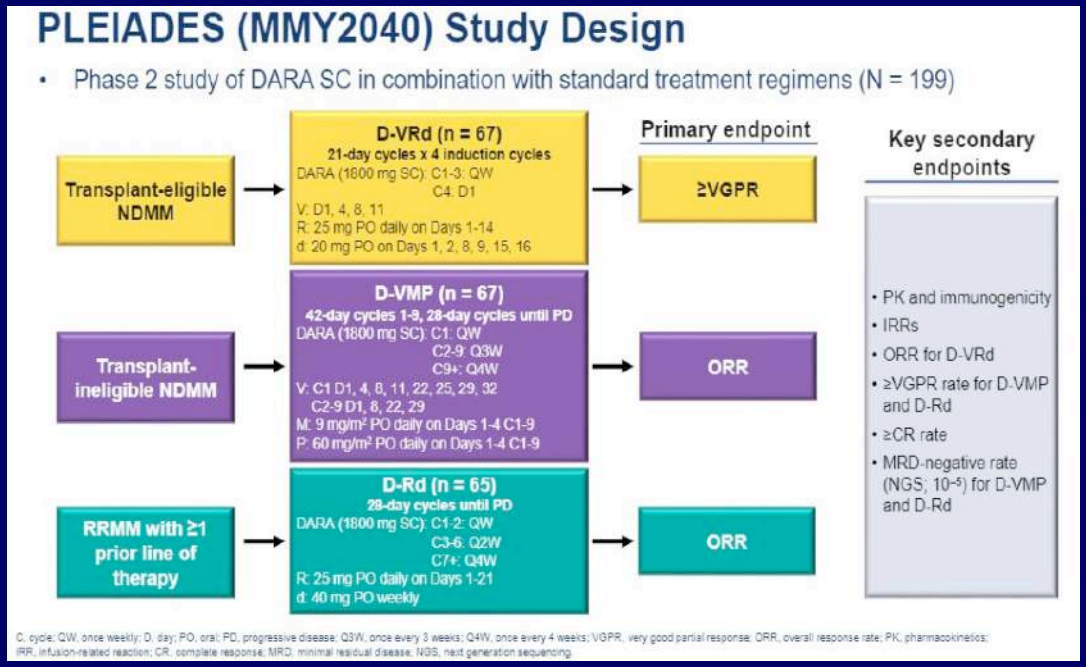


VRd-lite is well-tolerated and highly effective in TNE patients with robust PFS and OS.

MM, multiple myeloma; V, bortezomib; R, lenalidomide; d, dexamethasone; No., N, number.

O'Donnell et al, BJH 2018, 182(2):222-230;
O'Donnell et al, ASH 2019

Convenient treatment: Daratumumab sc



Dara sc combination therapy safety profiles were consistent with Dara iv with lower rate of IRRs

	D-VRd (n = 67)	D-VMP (n = 67)	D-Rd (n = 65)
	Transplant-eligible NDMM	*Transplant-ineligible NDMM*	*RRMM with ≥1 prior line of therapy*
Any TEAE, n (%)	67 (100.0)	67 (100.0)	65 (100.0)
Serious TEAE, n (%)	19 (28.4)	26 (38.8)	31 (47.7)
Grade 3/4 TEAE, n (%)	38 (56.7)	46 (68.7)	54 (83.1)
TEAEs leading to treatment discontinuation, n (%)	1 (1.5)	2 (3.0)	5 (7.7)
Fatal TEAE, n (%)	1 (1.5)	2 (3.0)	2 (3.1)

Chari et al., ASH 2019; abstract 3152

New standards including daratumumab in first line

Safety

ALCYONE study: D-VMP vs VMP

Adverse Events	D-VMP (n = 346)	VMP (n = 354)
Hematologic, n (%)		
Neutropenia	139 (40.2)	138 (39.0)
Thrombocytopenia	120 (34.7)	134 (37.9)
Anemia	60 (17.3)	70 (19.8)
Leukopenia	28 (8.1)	30 (8.5)
Lymphopenia	27 (7.8)	22 (6.2)
Nonhematologic, n (%)		
Pneumonia	45 (13.0)	15 (4.2)
Hypertension	19 (5.5)	6 (1.7)
Fatigue	12 (3.5)	9 (2.5)
Hyperglycemia	11 (3.2)	8 (2.3)
Diarrhea	9 (2.6)	11 (3.1)

Discontinuations due to AEs 6.9% vs 9.3%

MAIA study: D-Rd vs Rd

Adverse Events	D-Rd (n = 364)		Rd (n = 365)	
	Any grade[b]	Grade 3 or 4[c]	Any grade[b]	Grade 3 or 4[c]
Hematologic, n (%)				
Neutropenia	214 (59)	186 (51)	156 (43)	129 (35)
Anemia	134 (37)	49 (14)	143 (39)	75 (21)
Leukopenia	70 (19)	40 (11)	37 (10)	21 (6)
Lymphopenia	68 (19)	56 (15)	46 (13)	39 (11)
Nonhematologic, n (%)				
Diarrhea	221 (61)	25 (7)	174 (48)	19 (5)
Constipation	151 (42)	6 (2)	133 (36)	1 (<1)
Fatigue	152 (42)	31 (9)	105 (29)	15 (4)
Peripheral edema	142 (39)	7 (2)	109 (30)	2 (<1)
Back pain	134 (37)	11 (3)	99 (27)	13 (4)
Asthenia	121 (33)	18 (5)	95 (26)	15 (4)
Bronchitis	119 (33)	11 (3)	82 (23)	5 (1)
Nausea	121 (33)	5 (1)	85 (23)	2 (<1)
Insomnia	113 (31)	10 (3)	112 (31)	12 (3)
Pneumonia	88 (24)	53 (15)	51 (14)	33 (9)
Hypokalemia	80 (22)	37 (10)	65 (18)	35 (10)

Discontinuations due to AEs 9% vs 18%

The most common grade 3-4 AEs were neutropenia and pneumonia

Mateos MV et al ASH 2019; Bahlis N et al, ASH 2019

Ixazomib-Daratumumab-low dose dexamethasone

Phase II HOVON 143 trial

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

Median Age 76 years for unfit, 82 years for frail

	Unfit	Frail
ORR	74%	78%
PFS	23 months	12 months
Discontinuation	2%	7%
Early death	2%	9%
Grade 3-4 infections	9%	13%

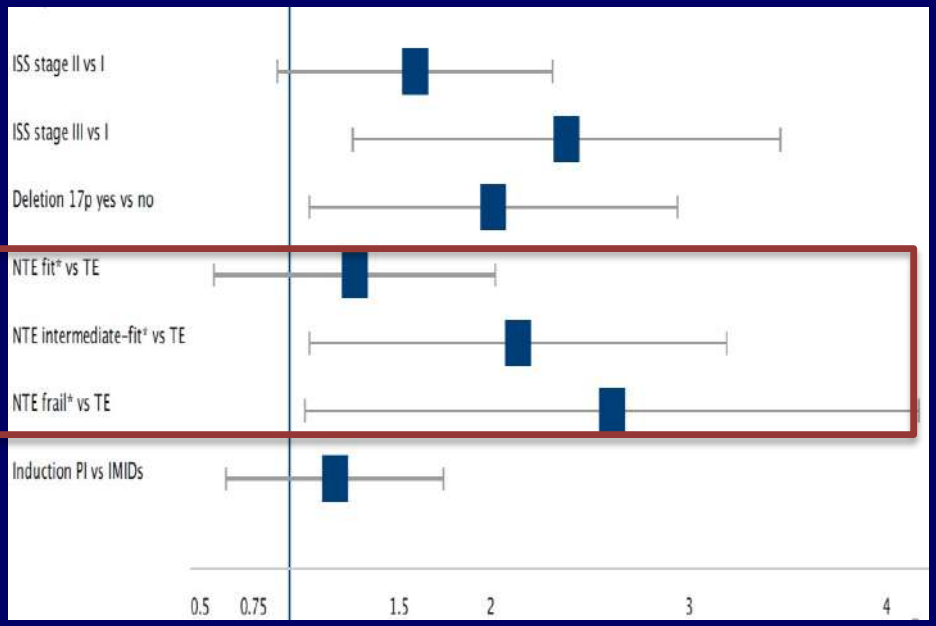
Effective and feasible treatment, however better identification and support of frail patients needed

Antibiotic and -viral prophylaxis: Cotrimoxazole 480 mg/day, Valaciclovir 500 mg tid Vaccinations

Zweegman et al., ASH 2019; abstract 695

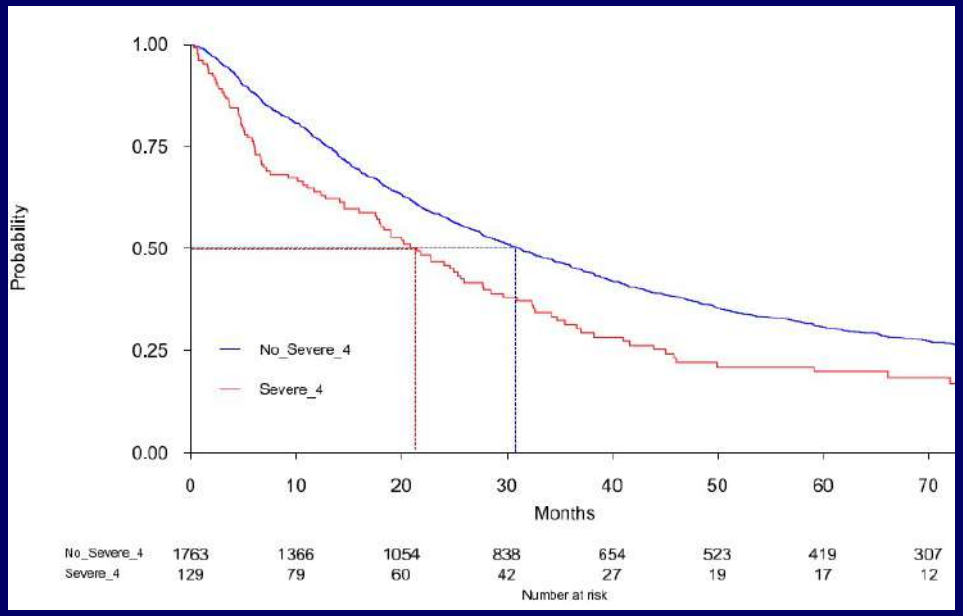
Managing toxicity in frail patients: infections

The risk of early severe infections is higher in intermediate fit/frail patients and negatively affects outcome



NO INFECTION **INFECTION**

PFS

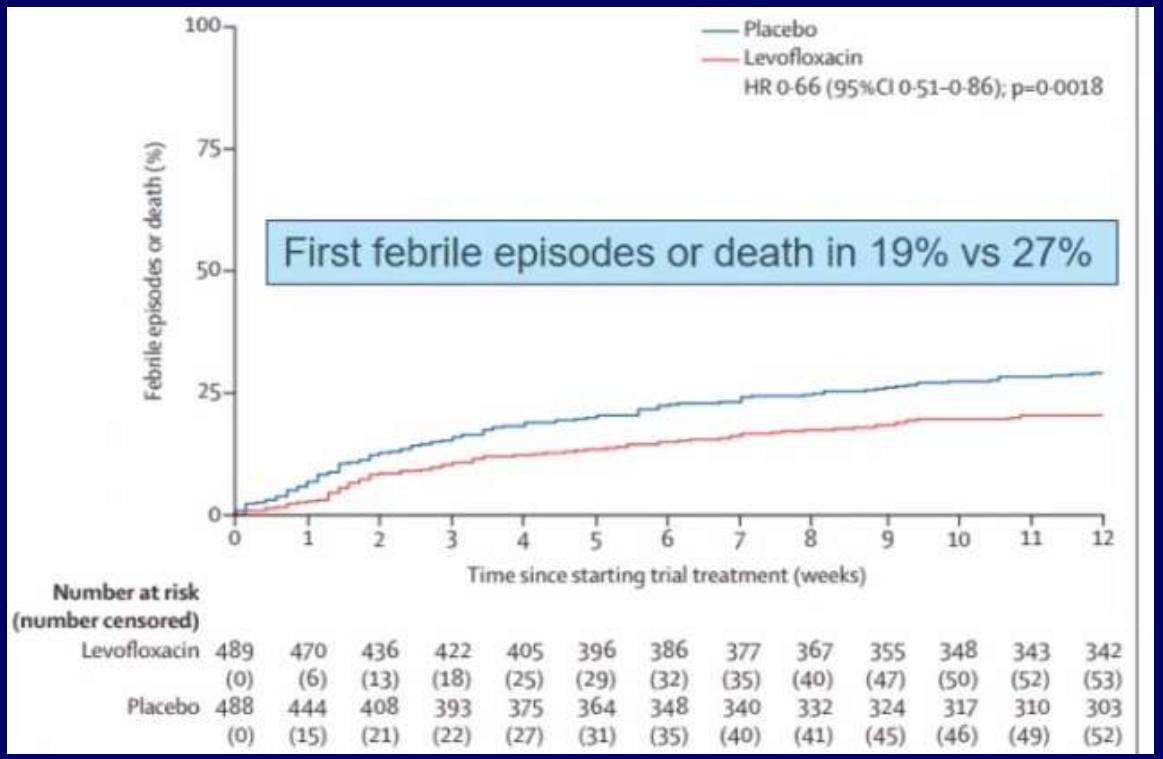


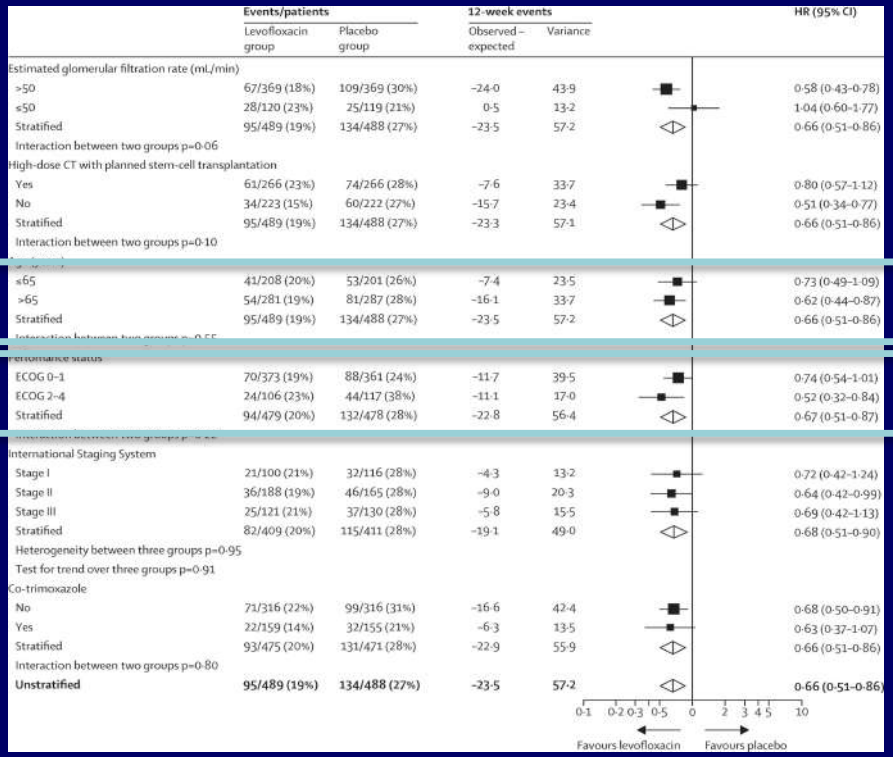
HR* 1.28, 95% CI 1.05-1.58, p 0.02

Bonello F et al, ASH 2020

Preventing toxicity
Antibiotic prophylaxis in newly diagnosed MM
TEAMM phase 3 trial

N= 977 NDMM. Oral levofloxacin 500 mg vs placebo for 12 weeks. Start within 2 weeks.





	Events/patients		12-week events		HR (95% CI)
	Levofloxacin group	Placebo group	Observed – expected	Variance	
Estimated glomerular filtration rate (mL/min)					
>50	67/369 (18%)	109/369 (30%)	-24·0	43·9	0·58 (0·43–0·78)
≤50	28/120 (23%)	25/119 (21%)	0·5	13·2	1·04 (0·60–1·77)
Stratified	95/489 (19%)	134/488 (27%)	-23·5	57·2	0·66 (0·51–0·86)
Interaction between two groups p=0·06					
High-dose CT with planned stem-cell transplantation					
Yes	61/266 (23%)	74/266 (28%)	-7·6	33·7	0·80 (0·57–1·12)
No	34/223 (15%)	60/222 (27%)	-15·7	23·4	0·51 (0·34–0·77)
Stratified	95/489 (19%)	134/488 (27%)	-23·3	57·1	0·66 (0·51–0·86)
Interaction between two groups p=0·10					
≤65	41/208 (20%)	53/201 (26%)	-7·4	23·5	0·73 (0·49–1·09)
>65	54/281 (19%)	81/287 (28%)	-16·1	33·7	0·62 (0·44–0·87)
Stratified	95/489 (19%)	134/488 (27%)	-23·5	57·2	0·66 (0·51–0·86)
ECOG 0–1	70/373 (19%)	88/361 (24%)	-11·7	39·5	0·74 (0·54–1·01)
ECOG 2–4	24/106 (23%)	44/117 (38%)	-11·1	17·0	0·52 (0·32–0·84)
Stratified	94/479 (20%)	132/478 (28%)	-22·8	56·4	0·67 (0·51–0·87)
International Staging System					
Stage I	21/100 (21%)	32/116 (28%)	-4·3	13·2	0·72 (0·42–1·24)
Stage II	36/188 (19%)	46/165 (28%)	-9·0	20·3	0·64 (0·42–0·99)
Stage III	25/121 (21%)	37/130 (28%)	-5·8	15·5	0·69 (0·42–1·13)
Stratified	82/409 (20%)	115/411 (28%)	-19·1	49·0	0·68 (0·51–0·90)
Heterogeneity between three groups p=0·95					
Test for trend over three groups p=0·91					
Co-trimoxazole					
No	71/316 (22%)	99/316 (31%)	-16·6	42·4	0·68 (0·50–0·91)
Yes	22/159 (14%)	32/155 (21%)	-6·3	13·5	0·63 (0·37–1·07)
Stratified	93/475 (20%)	131/471 (28%)	-22·9	55·9	0·66 (0·51–0·86)
Interaction between two groups p=0·80					
Unstratified	**95/489 (19%)**	**134/488 (27%)**	**-23·5**	**57·2**	**0·66 (0·51–0·86)**

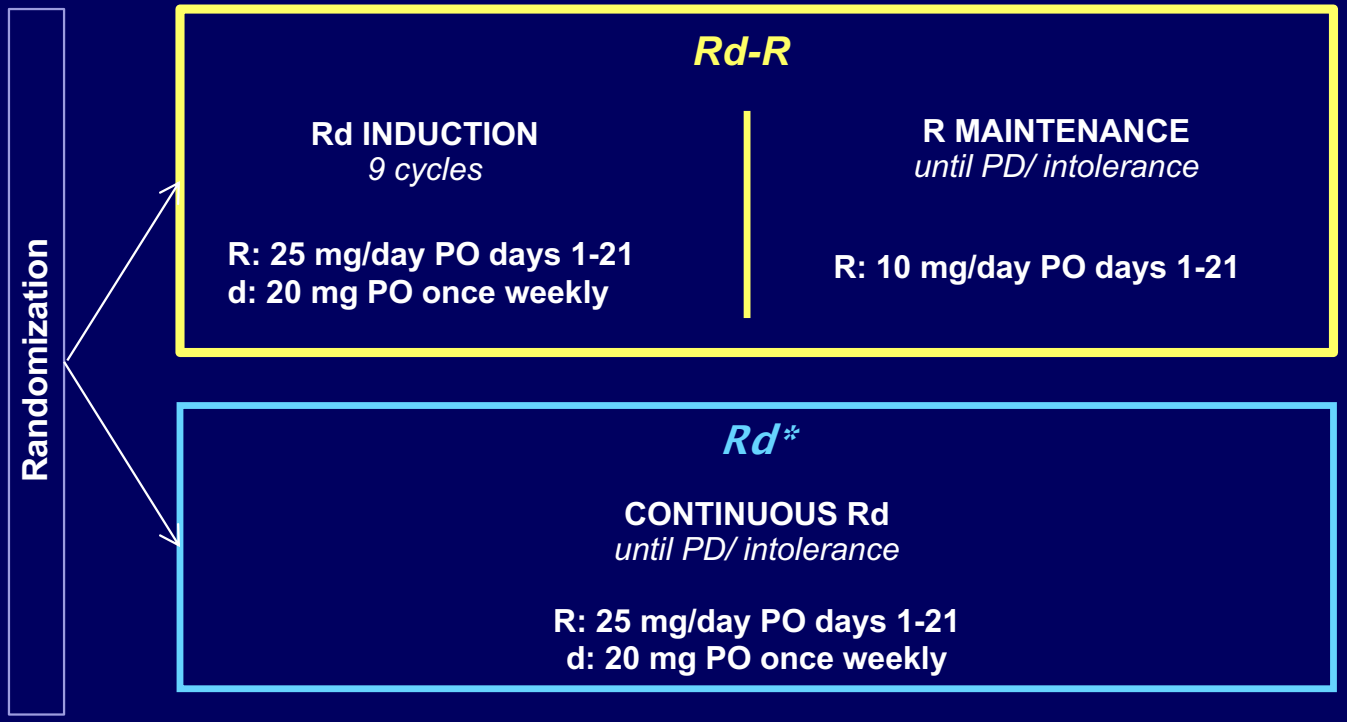
Prophylactic levofloxacin could be used for patients with newly diagnosed myeloma.

Drayson et al. Lancet Oncol 2019; 20:1760.

Dose/Schedule-Adjusted Rd-R vs continuous Rd in unfit patients

RV-MM-PI-0752 Phase III Randomized Study

199 intermediate-fit (unfit) patients have been enrolled and could be evaluated



*The dose and schedule of continuous Rd was the one adopted in patients >75 years in the FIRST trial (Hulin C et al. JCO 2016)

R, lenalidomide; d, dexamethasone; PO, orally; PD, progressive disease

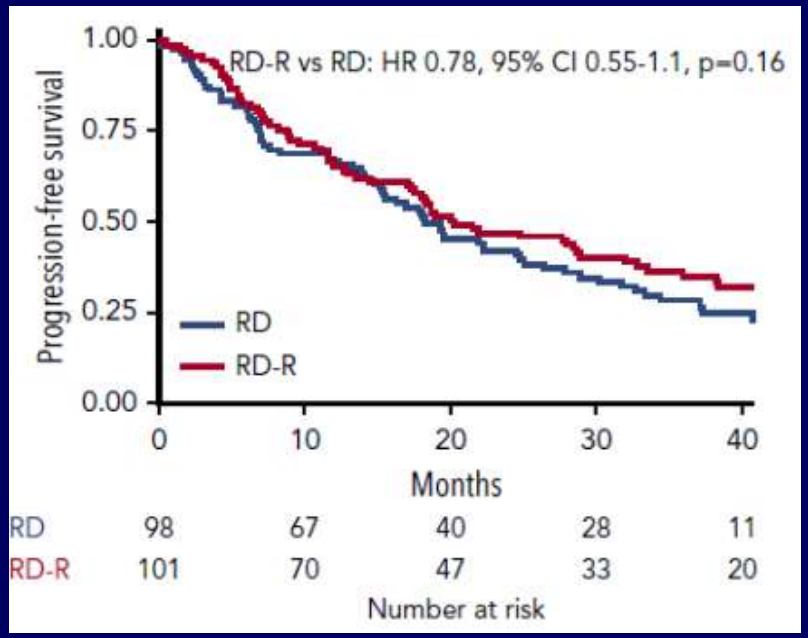
Larocca A, et al. ASH 2018, abstract 305

Dose/Schedule-Adjusted Rd-R vs Rd in unfit patients

Median follow-up 37 months

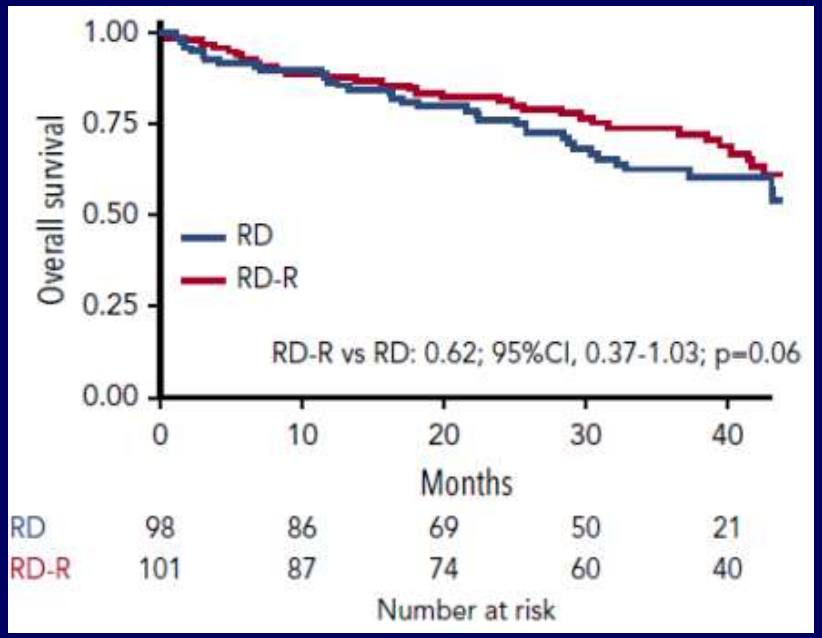
Progression-free survival

Median PFS 20.2 with Rd-R vs 18.3 months with Rd (HR, 0.78; 95% CI, 0.55-1.1; P 0.16).



Overall survival

Median OS not reached; 3-year OS rate 74% with Rd-R vs 63% with continuous Rd (HR, 0.62; 95% CI, 0.37-1.03; P 0.06).



Reduced dose intensity Rd-R and sparing steroid do not affect outcome in unfit patients

R, Lenalidomide; d, dexamethasone; PFS, progression-free survival, OS, overall survival.

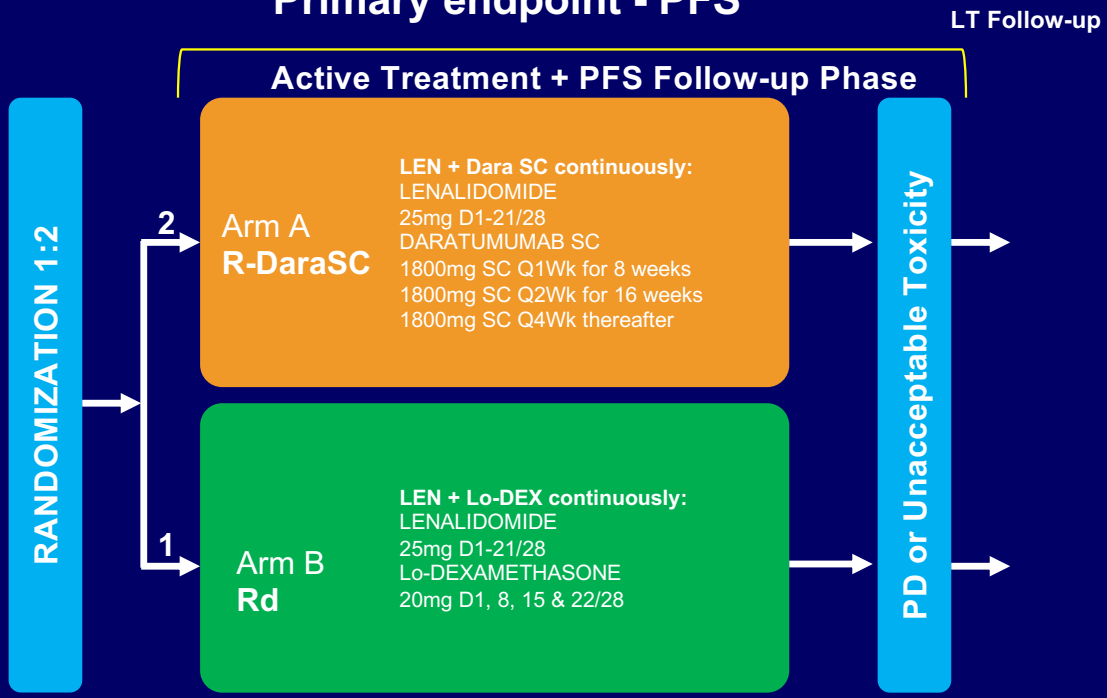
Larocca A, et al. VOLUME 137, NUMBER 22 3027-3036.

Frailty-adjusted treatments

IFM 2017-03

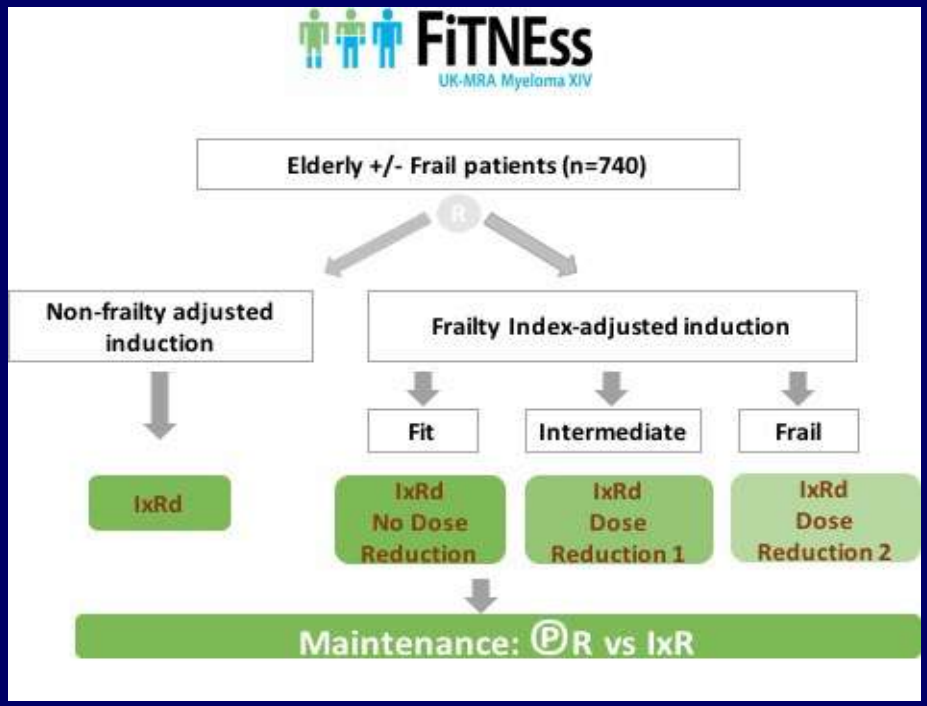
340 patients (frail)

Primary endpoint - PFS



UK-MRA FitNEss trial

Concept of frailty-adjusted dosing



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)

www.clincaltrials.gov identifier: NCT03993912

Fitness trial - NCT03720041

Conclusions
Frailty tailored treatment

FRAILTY ASSESSMENT IMWG Frailty Score		
FIT PATIENTS **(score 0)**	**INTERMEDIATE-FIT PATIENTS** **(score 1)**	**FRAIL PATIENTS** **(score ≥2)**
		
age ≤75 + ADL >4 + IADL >5 +CCI≤1	age 76-80 or ADL ≤4 or IADL ≤5 +CCI >1	age >80; age 76-80 + ADL ≤4 or IADL ≤5 or CCI >1; age ≤75 + at least 2 ADL ≤4 or IADL ≤5 or CCI >1
APPROVED REGIMENS **with possibile dose-adjustments according to frailty**		
• Daratumumab-VMP • Daratumumab-Rd • VRd • ASCT: Standard of care in ≤70 years old Consider in 71-75 years old* (*possibly with reduced conditioning)	• (Daratumumab)-VMP, consider weekly V • (Daratumumab)-Rd, consider dex discontinuation • Vd • VRd-lite	• Dose-adjusted Rd ± daratumumab • Dose-adjusted Vd • Palliative care
EXPERIMENTAL REGIMENS		
Daratumumab-VRd (NCT03652064) Isatuximab-VRd (NCT03319667) Belantamab-VRd (NCT04091126) KRD (NCT04096066) Ixazomib-RD (NCT018550524)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-VRd lite (NCT04052880) KRD (NCT04096066) Ixazomib-RD (NCT018550524)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-R (NCT03993912) Ixazomib-RD (NCT018550524)

Bonello F et al. Pharmaceuticals 2020

Acknowledgments

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