Highlights from
IMS 20th meeting 2023

Alessandra Larocca, MD, PhD

Strategie terapeutiche nel paziente “difficile-da-trattare“

Unfit-frail

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

Disclosures

Alessandra Larocca, MD, PhD

- **Honoraria**: Jansenn, Bristol Myers Squibb, Sanofi, GSK
- **Participation in advisory boards**: Jansenn, Bristol Myers Squibb, Sanofi, GSK

Not all elderly patients are equal

Heterogeneous population
Variety of disease- and host-related factors

Fit patients

Active, independent, exercise regularly

Unfit (intermediate) patients

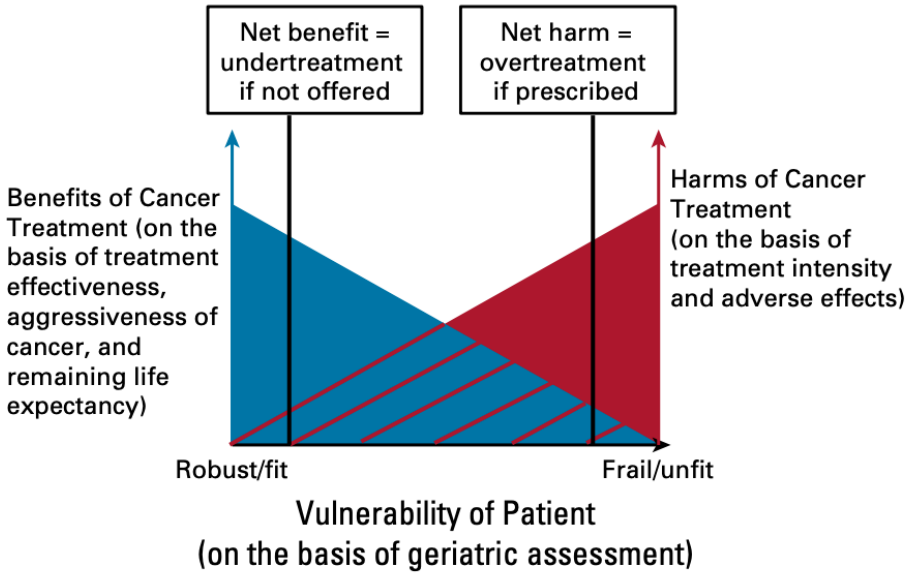
Can perform limited activities but they don't need any help

Frail patients

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

Personal communication.

Why do we need to identify the different subgroups of older adult with multiple myeloma?



Need to identify the more fragile population

Du Montier et al. JCO. 2021

Challenges for a frail patient

- Age and life expectancy
- Risk of toxicity (toxic deaths)
- Weakened immune system (increased risk of infections)
- Social barriers (care-giver)
- Quality of life
- Selection of the appropriate treatment

Challenges for a frail patient

- Age and life expectancy → ***identify frail patients***
- Risk of toxicity (toxic deaths)
- Weakened immune system (increased risk of infections)
- Social barriers
- Quality of life
- Selection of the appropriate treatment

Managing the older, frail patient with multiple comorbidities

Salomon MANIER
Professor of Hematology, Lille University Hospital

September 2023

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

⇒ **Frail patients have**
- **shorter OS and PFS times**
- **higher incidence of non-hematological AEs and treatment discontinuation**

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

The Simplified Frailty Index classifies more patients as frail, when compared to the gold-standard International Myeloma Working Group Frailty Index

K. Groen[1,2], F. Smits[1,2], K. Nasserinejad[3,4,5], M-D. Levin[6], J.C. Regelink[7], G-J. Timmers[8], E. de Waal[9], M. Westerman[10], G.A. Velders[11], K. de Heer[12], M.B.L. Leys[13], R.J.W. van Kampen[14], C.A.M. Stege[1,2,4], M.R. Seefat[1,2], I.S. Nijhof[1,15], E. van der Spek[16], S.K. Klein[7,17], N.W.C.J. van de Donk[1,2], P.F. Ypma[18], S. Zweegman[1,2]

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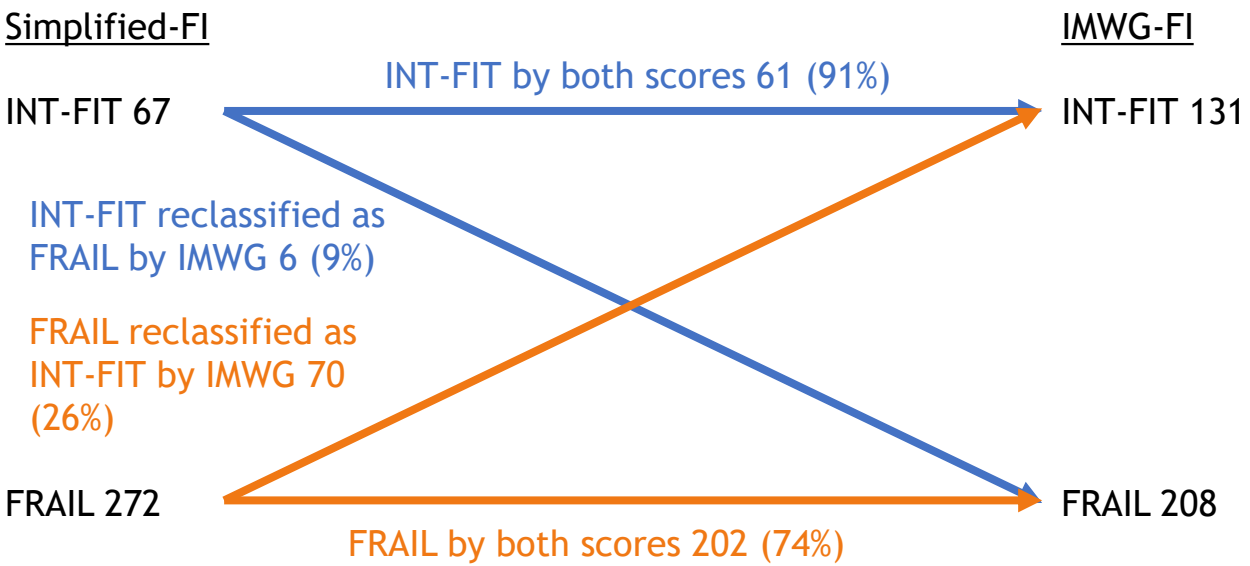
DHC 2024

Concordance rates

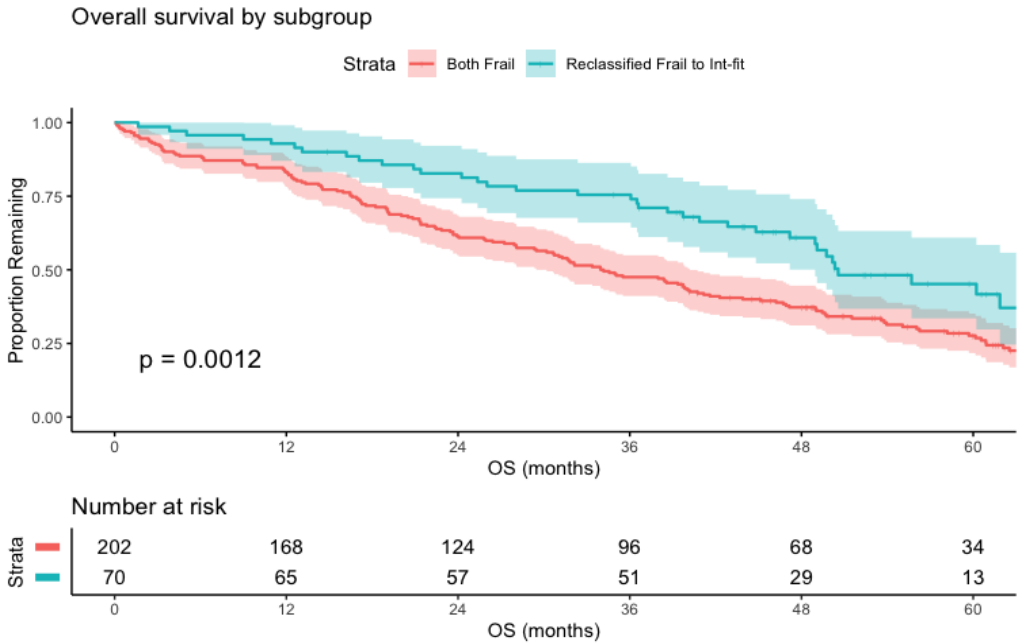
	IMWG-FI Intermediate-fit	IMWG-FI Frail
Simplified-FI Intermediate-fit	61 (18.0%)	6 (1.8%)
Simplified-FI Frail	70 (20.6%)	202 (59.6%)

22.4% of patients are classified differently

Reclassification

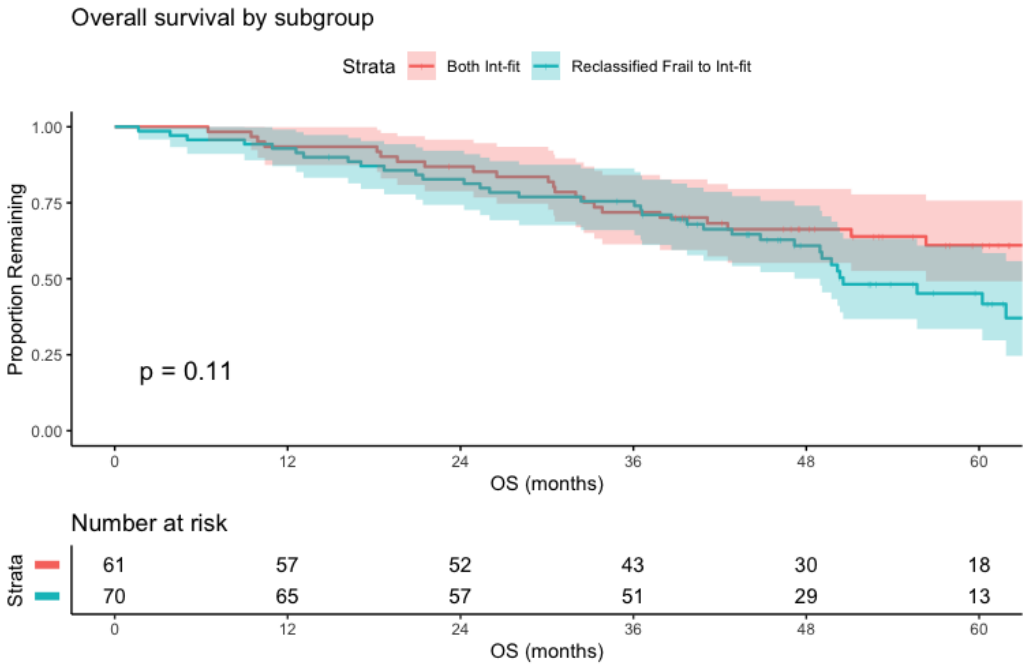


Are they frail?



Reclassified patients have significant superior overall survival compared with patients frail by both scores!

Or are they intermediate-fit?



Reclassified patients have the same overall survival compared with patients intermediate-fit by both scores!

Conclusion

- Over 20% of patients are classified differently between both scores
- Simplified-FI classifies more patients as frail, compared to the IMWG-FI
- IMWG-FI outperforms the Simplified-FI in predicting outcomes
- Potential risk of undertreating incorrectly classified patients
- Our study strongly advocates for the use of the IMWG-FI over de Simplified-FI

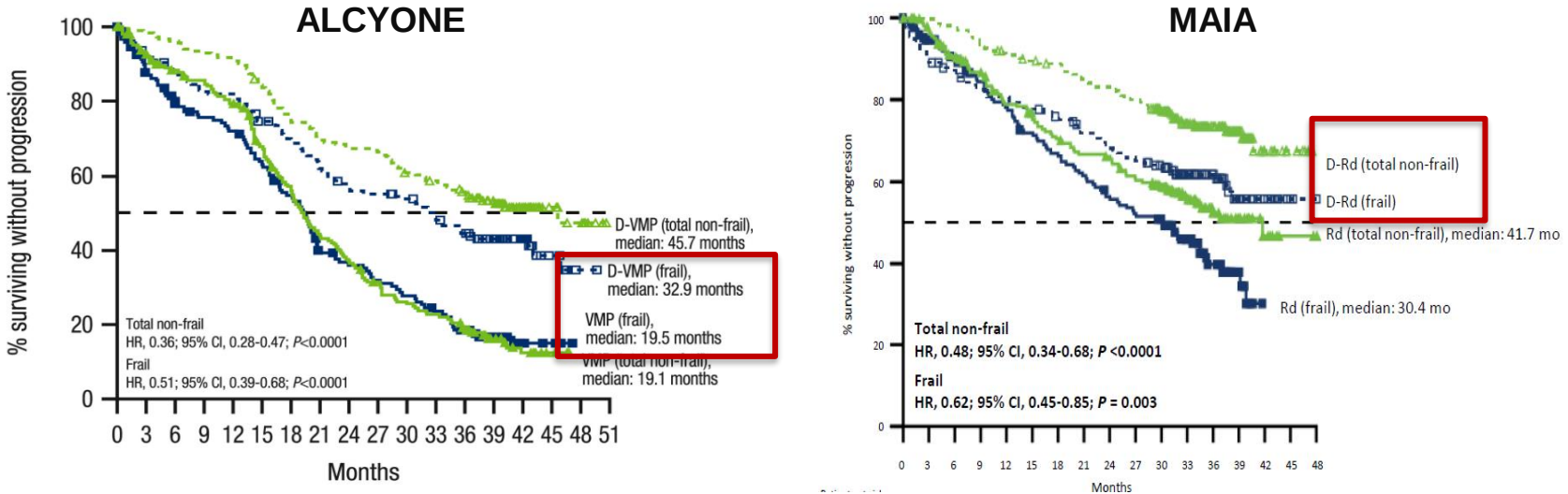
Challenges for a frail patient

- Age and life expectancy → ***identify frail patients***
- Risk of toxicity and toxic deaths →***less intensive treatments***
- Weakened immune system (increased risk of infections)
- Social barriers
- Quality of life
- Selection of the appropriate treatment

Daratumumab in first line

Impact of frailty on outcomes

Retrospective frailty assessment, using age, CCI (retrospective review of medical history), ECOG PS.
Frailty status was simplified into: **non-frail** (0–1; a combination of the fit and intermediate subgroups) and **frail** (≥2).



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

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

Frailty subgroup analysis of MAIA

	Fit (n=145)		Intermediate (n=250)		Frail (n=334)	
n (%)	D-Rd (n=68)	Rd (n=77)	D-Rd (n=128)	Rd (n=122)	D-Rd (n=168)	Rd (n=166)
Total number of patients with grade 3/4 TEAE	58 (85)	61 (79)	117 (91)	104 (85)	159 (95)	148 (89)
Hematologic						
Neutropenia	30 (44)	22 (29)	59 (46)	52 (43)	97 (58)	55 (33)
Lymphopenia	7 (10)	7 (9)	18 (14)	14 (12)	31 (19)	18 (11)
Anemia	4 (6)	11 (14)	17 (13)	24 (20)	28 (17)	40 (24)
Thrombocytopenia	4 (6)	3 (4)	8 (6)	12 (10)	17 (10)	18 (11)
Non-Hematologic						
Infections	16 (24)	22 (29)	46 (36)	30 (25)	70 (42)	46 (28)
Pneumonia	7 (10)	5 (7)	13 (10)	11 (9)	33 (20)	17 (10)
Pulmonary embolism	8 (12)	5 (7)	6 (5)	9 (7)	7 (4)	5 (3)
Patients who discontinued treatment	20 (29)	45 (58)	45 (35)	74 (61)	78 (45)	114 (68)
Reason for discontinuation						
Progressive disease	14 (21)	21 (27)	25 (20)	35 (29)	32 (19)	43 (25)
Adverse event	5 (7)	12 (15)	9 (7)	21 (17)	17 (10)	32 (19)
Non-compliance	1 (1)	4 (5)	5 (4)	7 (6)	8 (5)	12 (7)
Death	0	2 (3)	5 (4)	3 (2)	18 (11)	15 (9)

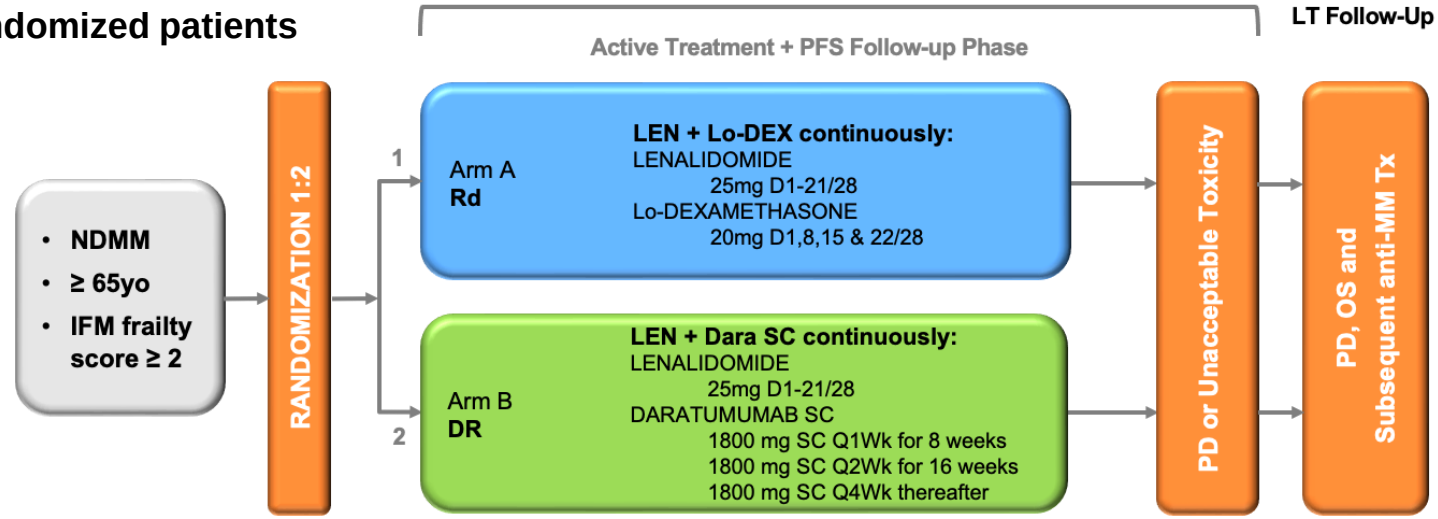
Zweegman et al., EMN 2021

Steroid sparing regimen including daratumumab for frail MM patients

IFM 2017-03

Dara-R vs Rd

295 randomized patients



Randomization stratified by ISS (I vs II vs III) and age (<80 vs ≥80)
In Arm B low-dose dex (20mg/week) during Cycle 1 and 2 (with SC dara)

NCT03993912

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 more side effects

IFM 2017-03 – Patients characteristics

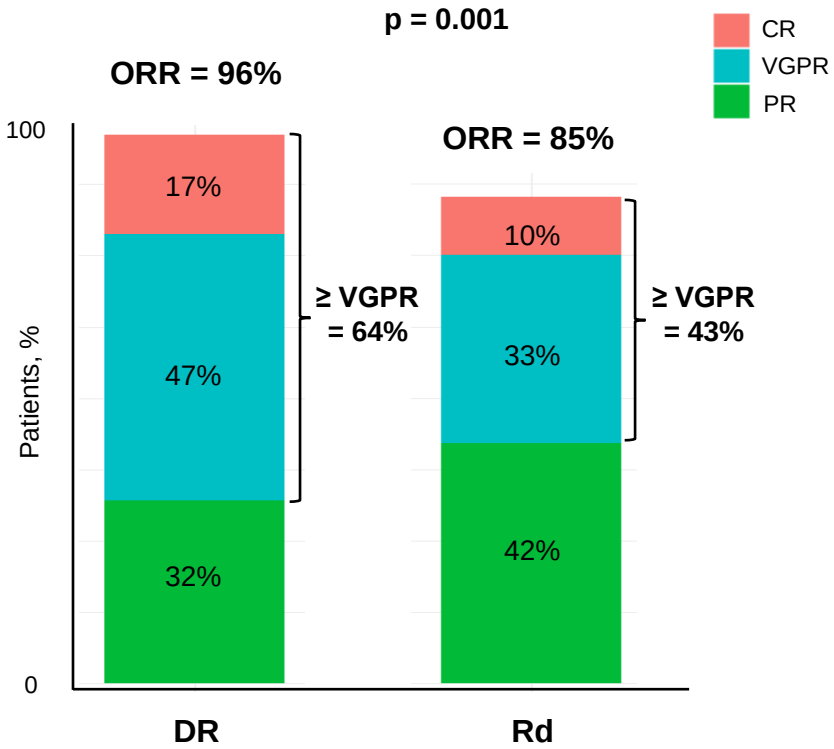
Characteristics	DR group (N=199)	Rd group (N=94)
Median age (range) - yr	81 (68-92)	81 (68-90)
Age category – no. (%)		
65 to < 70 yr	2 (1%)	2 (2%)
70 to < 75 yr	30 (15%)	13 (14%)
75 to < 80 yr	49 (25%)	19 (20%)
≥ 80 yr	118 (59%)	61(65%)
Sex - no. (%)		
Female	101 (51%)	48 (51%)
Male	98 (49%)	46 (49%)
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%)

Characteristics	DR group (N=199)	Rd group (N=94)
ISS disease stage – no. (%)		
I	33 (17%)	18 (19%)
II	102 (51%)	49 (53%)
III	64 (32%)	26 (28%)
NA	0	1
Type of measurable disease – no (%)		
IgG	113 (57%)	49 (52%)
IgA	38 (19%)	20 (21%)
PBJ only	21 (11%)	10 (11%)
SFLC only	27 (14%)	15 (16%)
Cytogenetics profile* – no (%)		
Standard risk	148 (83%)	60 (78%)
High risk	31 (17%)	17 (22%)
NA	20	17
del17p	16 (9%)	11 (14%)
t(4;14)	9 (5%)	5 (6%)
t(14;16)	6 (3%)	3 (3%)
Creatinine clearance – no. (%)		
< 30mL/min	1 (1%)	3 (3%)
30 to < 60mL/min	119 (60%)	50 (53%)
≥ 60 mL/min	79 (40%)	41 (44%)

* del17p, t(4;14), t(14;16)

Manier S et al; Abs 569 ASH 2022,

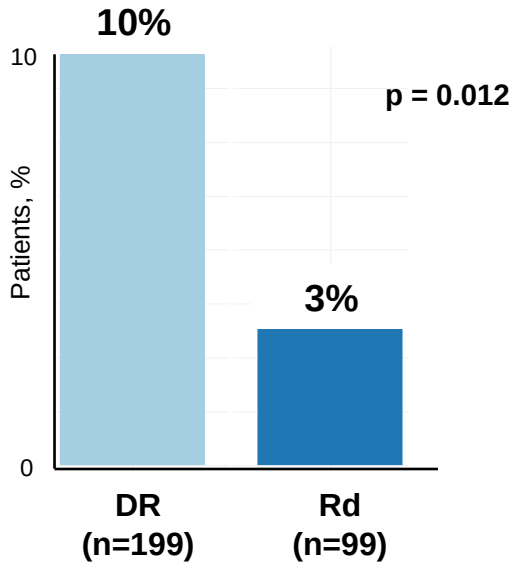
IFM 2017-03 – Best response rate and MRD



Best overall response rate was significantly higher with DR

MRD at 10^{-5} by NGS, in ITT analysis

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



DR improved rates of MRD negativity at 10^{-5} *vs.* Rd

Manier S et al; Abs 569 ASH 2022,

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	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

Manier S et al; Abs 569 ASH 2022,

SAFETY AND CLINICAL ACTIVITY OF BELANTAMAB MAFODOTIN PLUS LENALIDOMIDE AND DEXAMETHASONE IN TRANSPLANT INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: THE PHASE 1/2 BELARD STUDY

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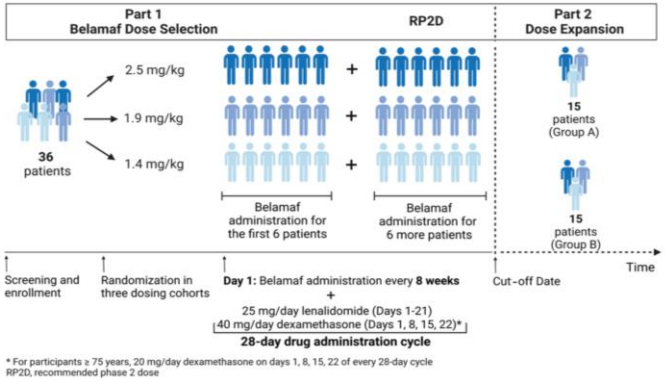
[1]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece
[2]Health Data Specialists, Dublin, Ireland

P-123

Study Design

- The BelaRd study (NCT04808037) is a phase 1/2 clinical trial being conducted in Greece and is designed to enroll 66 patients with NDMM who are not eligible for transplant.
- This report focuses on Part 1 of the study, which evaluates the safety and tolerability of three different doses of Belamaf (2.5 mg/kg, 1.9 mg/kg and 1.4 mg/kg) in combination with Rd in 36 patients.



* For participants ≥ 75 years, 20 mg/day dexamethasone on days 1, 8, 15, 22 of every 28-day cycle
RP2D, recommended phase 2 dose

- The primary objective of this Part 1 analysis is to determine the recommended dose for phase 2 (RP2D), with the cut-off date for data analysis being 05 June 2023.
- In this phase, Belamaf will initially be administered every 8 weeks (Q8W), and depending on observed toxicity, dosing may be adjusted to every 12 weeks (Q12W).

Baseline Characteristics

	Cohort 1 (2.5 mg/kg Q8W) (n=12)	Cohort 2 (1.9 mg/kg Q8W) (n=12)	Cohort 3 (1.4 mg/kg Q8W) (n=12)
Age in years, median (range)	75.0 (66.0-86.0)	74.5 (68.0-82.0)	69.0 (64.0-79.0)
Gender, n (%)			
Male	8 (66.7)	5 (41.7)	6 (50.0)
Female	4 (33.3)	7 (58.3)	6 (50.0)
ECOG PS, n (%)			
0	4 (33.3)	3 (25.0)	8 (66.7)
1	6 (50.0)	9 (75.0)	4 (33.3)
2	2 (16.7)	0 (0.0)	0 (0.0)
R-ISS, n (%)			
I	1 (8.3)	2 (16.7)	3 (25.0)
II	9 (75.0)	10 (83.3)	8 (66.7)
III	2 (16.7)	0 (0.0)	1 (8.3)
Lytic Bone Lesions, n (%)	7 (58.3)	7 (58.3)	5 (41.7)
High-risk Cytogenetics*, n (%)	1 (8.3)	2 (16.7)	0 (0.0)
IMWG Frailty Score, n (%)			
Fit (score =0)	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate-fitness (score=1)	10 (83.3)	11 (91.7)	11 (91.7)
Frail (score ≥ 2)	2 (16.7)	1 (8.3)	1 (8.3)

*High risk cytogenetics defined as Del 17p, t(14:16) or t(4:14)
ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMWG, International Myeloma Working Group; R-ISS, Revised International Staging System

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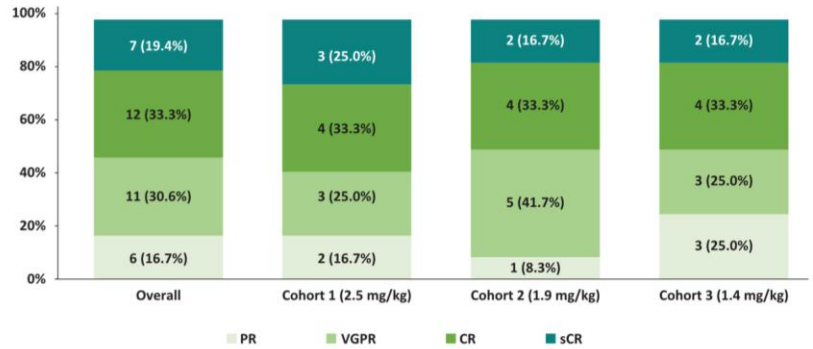
P-123

Clinical Activity

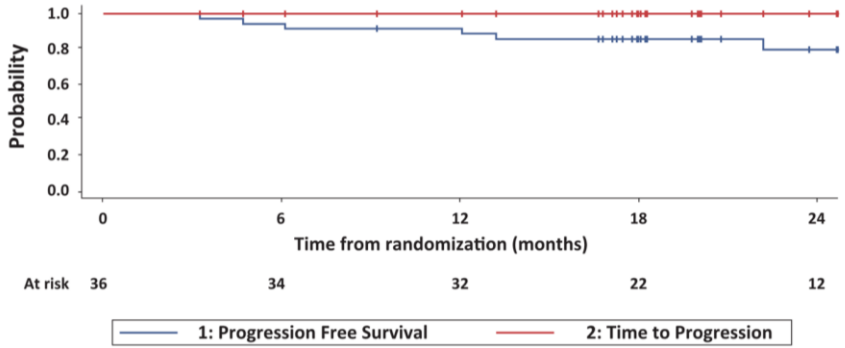
Best Response Overall and by Cohort



	Overall	Cohort 1	Cohort 2	Cohort 3
Time to first response (months), median (min-max)	1.0 (0.9-3.8)	1.1 (1.0-2.1)	1.0 (0.9-3.8)	1.0 (1.0-2.0)
Time to CR (months), median (min-max)	13.4 (2.8-24.8)	11.5 (4.4-23.1)	13.0 (2.8-18.0)	14.8 (10.4-24.8)
Time to VGPR (months), median (min-max)	11.9 (2.8-24.8)	11.5 (2.9-23.1)	12.2 (2.8-18.0)	13.2 (2.8-24.8)

CR, Complete Response; PR, Partial Response; sCR, stringent Complete Response; VGPR, Very Good Partial Response

Progression Free Survival and Time to Progression



- 100% overall response rate
- No disease progression
- Median time to first response: ~1 month
- Median follow-up: 20.3 months

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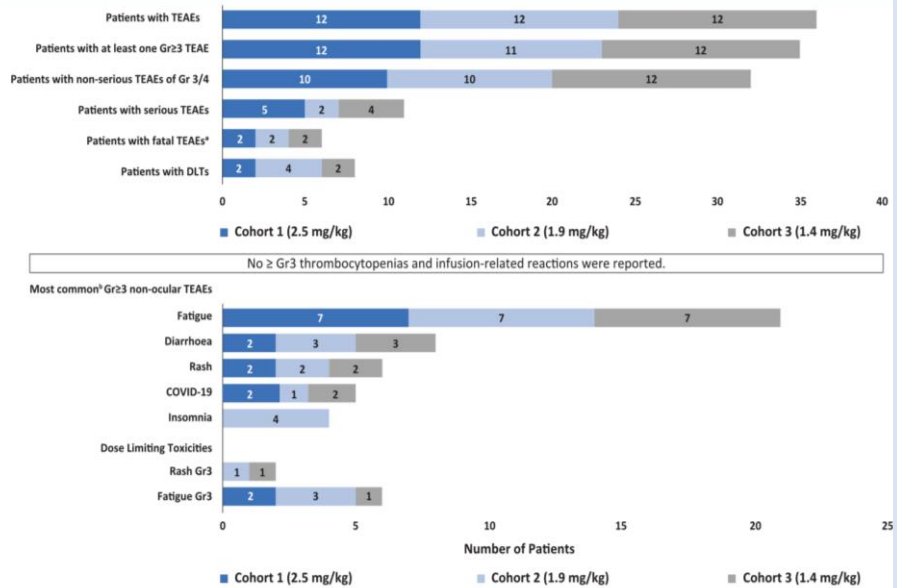
P-123

Safety Profile



No ≥ Gr3 thrombocytopenias and infusion-related reactions were reported.

Ocular Assessments

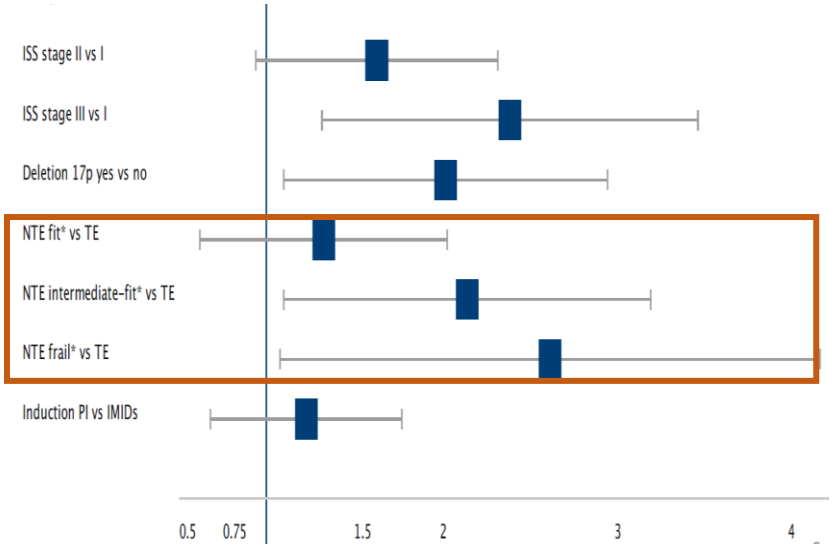
	Cohort 1 (2.5 mg/kg Q8W)	Cohort 2 (1.9 mg/kg Q8W)	Cohort 3 (1.4 mg/kg Q8W)
Ocular Symptoms, n (%)			
Grade 0-1	116 (54.0%)	150 (61.2%)	122 (58.9%)
Grade 2	87 (40.5%)	86 (35.1%)	78 (37.7%)
Grade 3-4	12 (5.6%)	9 (3.7%)	7 (3.4%)
Keratopathy, n (%)			
Grade 0-1	179 (82.9%)	214 (87.3%)	185 (89.4%)
Grade 2	28 (13.0%)	30 (12.2%)	21 (10.1%)
Grade 3-4	9 (4.2%)	1 (0.4%)	1 (0.5%)
Decreased Vision[a], n (%)			
Grade 0-1	84 (39.3%)	136 (55.7%)	117 (56.5%)
Grade 2	94 (43.9%)	76 (31.1%)	65 (31.4%)
Grade 3-4	36 (16.8%)	32 (13.1%)	25 (12.1%)

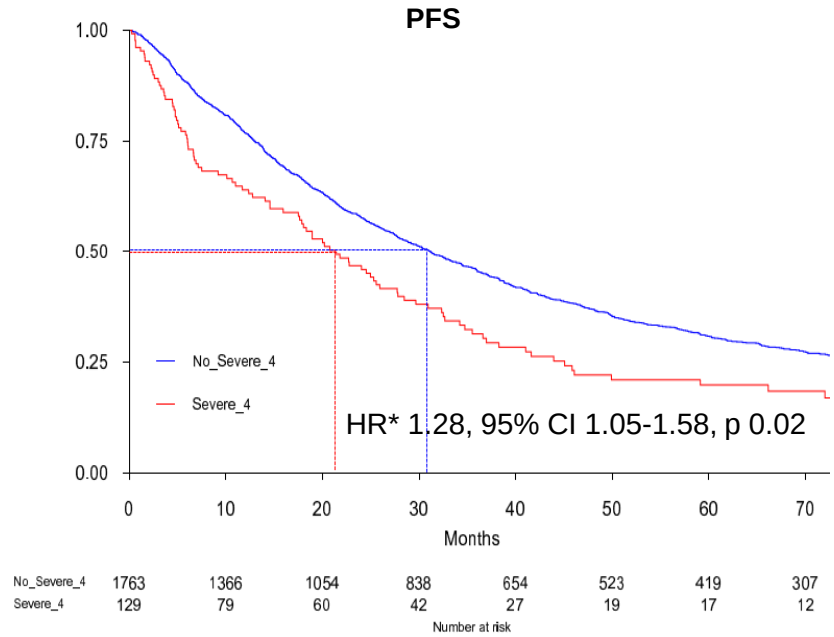
[a] Decreased Vision in this analysis describes any event suggesting visual acuity deterioration; it corresponds to the following MedDRA terms: vision blurred, visual acuity reduced and visual impairment. The maximum grade of the aforementioned terms is presented.

Challenges for a frail patient

- Age and life expectancy → ***identify frail patients***
- Risk of toxicity and toxic deaths →***less intensive treatments***
- Weakened immune system and increased risk of infections →***prophylaxis***
- Social barriers
- Quality of life
- Selection of the appropriate treatment

Risk of infections in frail patients





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

Bonello F et al, ASH 2020

Optimizing supportive care management

Evangelos Terpos, MD, PhD
Professor of Hematology, Director of SC Transplant Unit,
Plasma Cell Dyscrasias Unit, Department of Clinical Therapeutics,
National and Kapodistrian University of Athens,
School of Medicine, Athens, Greece

Infections is a Severe Problem for Myeloma Patients

- **Infection remains the leading cause of death in patients with multiple myeloma (MM).** Several factors account for this infectious risk: the net state of immunosuppression from MM and its treatment, age and comorbidities such as renal failure and frailty.
- The periods of **highest infectious risk are during the first three months after diagnosis** and when treating RRMM.
- Newly diagnosed patients have higher rates of potentially preventable infections (e.g., *Streptococcus pneumoniae, Haemophilus Influenzae)*.
- Most infections are caused by viruses and bacteria. Bacterial infections manifest, most commonly as pneumonia and bacteremia. Viral infections present typically as seasonal viruses particularly influenza, SARS-CoV-2 and herpes zoster.

International Myeloma Society

Raje N, et al. Lancet Haematol 2022;9:143-61

Prophylaxis for Infections in Myeloma Patients – IMWG Recommendations

- During periods of increased infectious risk, antibacterial prophylaxis with **levofloxacin** may be considered.

- **Acyclovir** prophylaxis is used for patients who are seropositive for herpes simplex virus and varicella zoster virus if tested. We also use acyclovir prophylaxis for patients treated with proteasome inhibitors or MM-targeted monoclonal antibodies, specifically CD38 directed moAbs.

- We reserve **trimethoprim-sulfamethoxazole** for patients at risk of *pneumocystis jiroveccii* pneumonia (RRMM or receipt of high doses of dexamethasone such as ≥ 40mgs/day for 4 days/wk). Alternatives such as dapsone may be considered for patients with sulfa allergies.

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Raje N, et al. Lancet Haematol 2022;9:143-61

Vaccination for Myeloma Patients – IMWG Recommendations

- We immunize patients with MM with **yearly inactivated influenza vaccine** (preferably with a two-dose series of high-dose influenza vaccine, regardless of age) and **inactivated *S. pneumoniae* vaccines:** Pneumococcal 13 - valent conjugate (PCV13, Prevnar) followed by Pneumococcal 23-Valent polysaccharide (PPSV23, Pneumovax) every 5 years. **We only recommend inactivated vaccines**.

- Single-agent lenalidomide improves response to vaccination in patients with MM provided dexamethasone is not given concurrently.

- After ASCT, patients with MM may lose their immunity to the pathogens against which they were vaccinated. These patients should be re-vaccinated 6-24 months after ASCT. Recent data suggest that immunization with recombinant zoster vaccine [RZV; Shingrix] is safe and effective post-ASCT. We thus recommend RZV vaccination post-ASCT.

- **We recommend the extension of RZV in all MM patients. We recommend continued use of VZV prophylaxis, where indicated, despite vaccination.**

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Raje N, et al. Lancet Haematol 2022;9:143-61

Infections Prophylaxis – Other Measures

- We recommend the use of passive immunization to patients with MM after exposure to individuals with hepatitis A, varicella, or measles.
- We recommend that **household contacts receive routine vaccinations with inactivated vaccines**, and that MM patients avoid close contact with recipients of live vaccines, when possible.
- We encourage **healthcare providers** caring for patients with MM to receive all indicated immunizations, particularly **the seasonal influenza viruses**.
- **The use of intravenous immunoglobulin** is reserved for very specific situations such as life threatening infections and **an IgG level of less than 400mg/dl with recurrent infections or under T-cell engagers targeting anti-BCMA.**
- For travelers to endemic areas of infection, we consider travel vaccines and antimicrobial prophyalxis and recommend a consultation with an infectious disease specialist or a travel clinic.

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Raje N, et al. Lancet Haematol 2022;9:143-61

COVID-19: Prophylaxis and Treatment (updated EMN guidelines)

MM and COVID-19 vaccination

- Booster vaccines for SARS-CoV-2 should be administered to all patients with MM.
- Variant-specific booster vaccines, such as the bivalent vaccine for the ancestral Wuhan strain and the Omicron BA.4/5 strains, are important for COVID-19 protection, as novel strains emerge and become dominant in the community.
- Boosters should be administered 6–12 months after the last vaccine shot or documented COVID-19 infection (hybrid immunity). A 6–12 month interval between each booster dose is reasonable. It is unknown if boosters with the same vaccine are effective against the new virus strains.
- If possible, vaccination should be performed before the initiation of B-cell depleting therapies (CD38- or BCMA-targeting treatments). Booster shots seem to overcome the negative effect of anti-CD38 monoclonal antibodies, but not of anti-BCMA treatments, on humoral responses.

Treatment of patients with MM and COVID-19

- Oral antivirals nirmatrelvir/ritonavir (Paxlovid) or molnupiravir (Lagevrio) can be offered to all MM outpatients with mild to moderate COVID-19 regardless vaccination or disease status, as soon as possible after the positive test for SARS-CoV-2 and within 5 days of COVID-19-related symptom onset. Careful consideration of drug interactions is essential. Nirmatrelvir/ritonavir is preferred over molnupiravir.
- Remdesivir can be administered intravenously both in the outpatient and the inpatient setting. For patients who cannot receive nirmatrelvir/ritonavir, the use of remdesivir is recommended.
- Oral antivirals and remdesivir remain effective against Omicron subvariants BA.2.12.1, BA.4, BA.5, BQ.1.1, XBB and XBB.1.5.
- High-titer convalescent plasma may improve patient outcomes; however, it is extremely difficult to have convalescent plasma against the novel mutants and, thus, its value is debatable in the post-pandemic era.
- Myeloma treatment should be interrupted and re-initiated upon symptom resolution.

International Myeloma Society

Terpos E, et al. Leukemia 2023;37(6):1175-1185

Challenges for a frail patient

- Age and life expectancy → ***identify frail patients***
- Risk of toxicity and toxic deaths →***less intensive treatments***
- Weakened immune system and increased risk of infections →***prophylaxis***
- Social barriers →***patient preference and convenience***
- Quality of life
- Selection of the appropriate treatment

Social barriers in real life

- **Greater use of welfare services**
  - possibility of controlling the disease for long periods determines a change in care models with the need for frequent access to hospital, often for the patient's entire lifespan

- **Need for a care-giver**
  - dependence on others in the activities of daily living, in some cases absence of a care-giver or single care-giver of working age

- **Travel burden for patients and caregivers**
  - proximity to care is crucial to guarantee better outcomes and quality of life for both patients and their caregivers, and more equitable and sustainable healthcare.

Patient-defined goals and preferences

Older adults with cancer starting chemotherapy

Attitude scale (n = 121)

Item	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
The most important thing to me **is living as long as I can,** no matter what my QoL is	13%	12%	17%	34%	22%
I would rather live a shorter life than lose my ability to **take care of myself**	28%	31%	16%	13%	7%
Maintaining my **thinking ability** is more important than living as long as possible	41%	40%	14%	2%	1%

Enrique Soto Perez De Celis, et al. J Clin Oncol 2018;36(15_suppl): ASCO abstract 10009

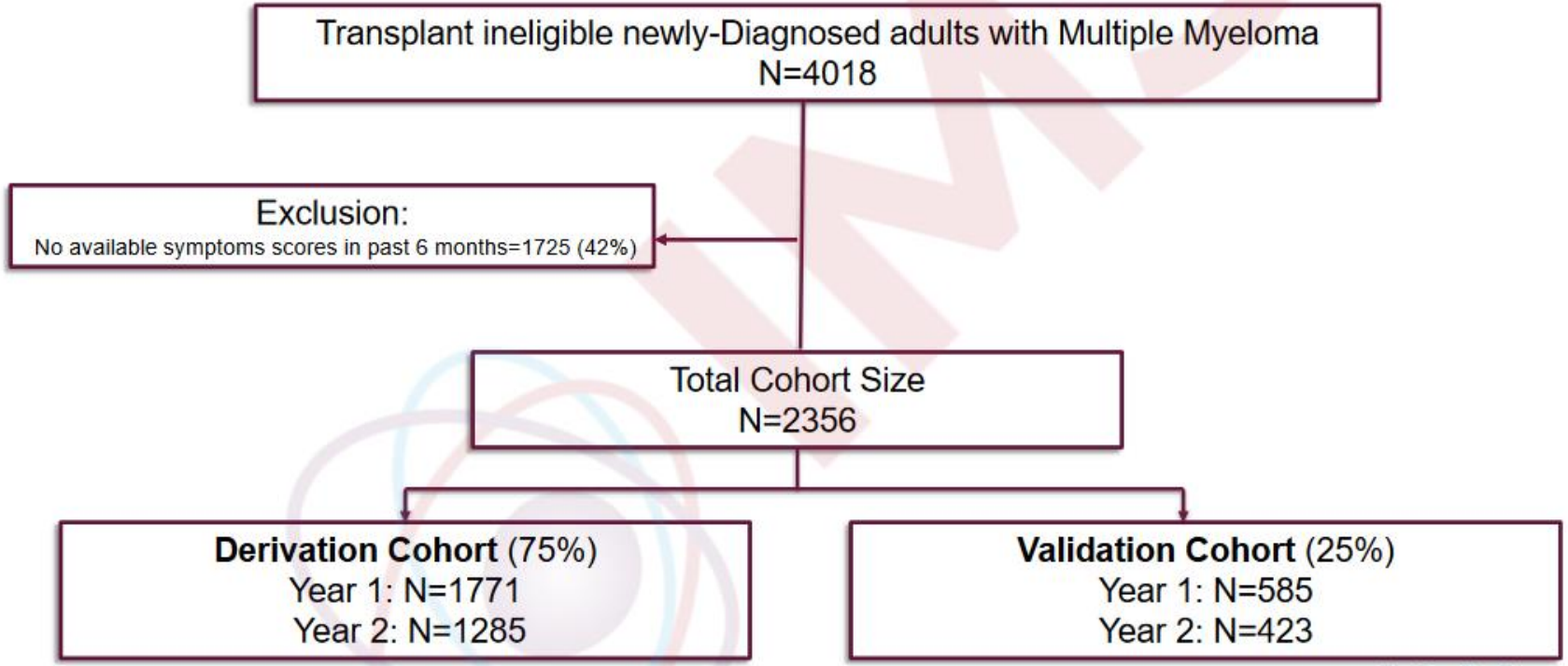
Development and Validation of a Prognostic Survival Model incorporating Patient Reported Outcome among Transplant Ineligible patients with Multiple Myeloma

Hira S Mian, Rinku Sutradhar, Matthew Cheung, Anastasia Gayowsky, Jason Tay, Amaris Balitsky, Tanya Wildes, Arleigh McCurdy, Alissa Visram, Irwindeep Sandhu, Hsien Seow

Background

- Over 50% of patients with hematologic malignancies have a discordant understanding of their prognosis
- Multiple prognostic tools have been developed in MM but are limited by:
    1) Developed for health care providers and include specialized tests
    2) Used at the time of diagnosis and do not account for changing variables
- Incorporating patient reported outcomes may represent an opportunity for improving prognostic tools that can be used by patients
    - Databases within Ontario, Canada represent a unique opportunity due to the implementation of standardized cancer symptom assessment in clinics
    - Edmonton Symptom Assessment Score (ESAS) consists of 9 symptoms

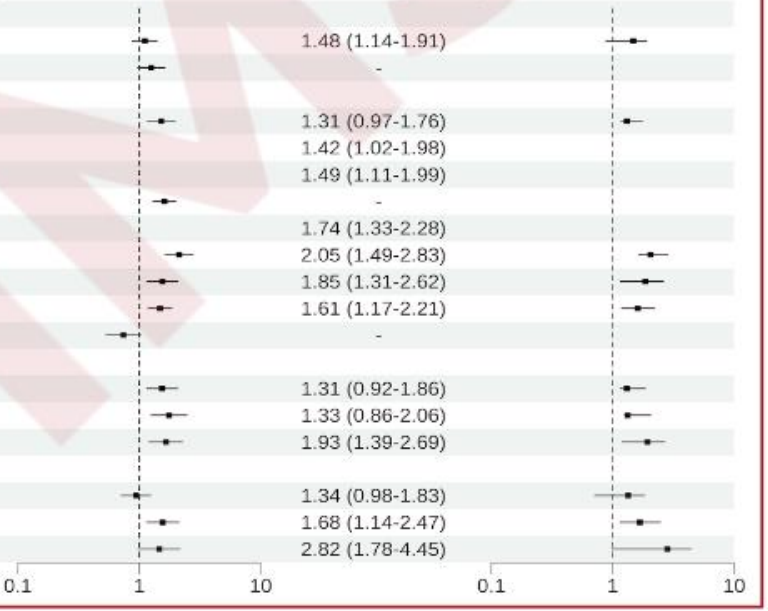
Study Cohort Selection



Development and Validation of a Prognostic Survival Model incorporating Patient Reported Outcome among Transplant Ineligible patients with Multiple Myeloma

Median Age 75 years

Variable	Year 1 (N=1,770) Hazard Ratio (95% CI)	Year 2 (N=1,282) Hazard Ratio (95% CI)
Age at index >=80 years	1.11 (0.88-1.41)	1.48 (1.14-1.91)
Distance >=50km to the nearest cancer centre at index	1.25 (0.97-1.63)	-
Comorbidities 5 years prior		
CHF	1.52 (1.17-1.98)	1.31 (0.97-1.76)
Hypertension	-	1.42 (1.02-1.98)
Previous other cancer up to 15 years prior	-	1.49 (1.11-1.99)
CRAB 6 months prior to 6 months post diagnosis	1.61 (1.29-2.01)	-
Hemoglobin <100g/L	-	1.74 (1.33-2.28)
Hospitalization in 6 months prior	2.13 (1.63-2.78)	2.05 (1.49-2.83)
ER visit in 6 months prior	1.55 (1.16-2.08)	1.85 (1.31-2.62)
Radiation 12 months prior	1.48 (1.18-1.86)	1.61 (1.17-2.21)
Novel drugs 12 months prior	0.74 (0.53-1.03)	-
Functional score (reference = 0/1)		
2	1.54 (1.16-2.06)	1.31 (0.92-1.86)
3 or 4	1.76 (1.25-2.48)	1.33 (0.86-2.06)
Missing	1.66 (1.20-2.28)	1.93 (1.39-2.69)
Count of high ESAS scores (reference = 0)		
1-3	0.94 (0.71-1.24)	1.34 (0.98-1.83)
4-6	1.56 (1.15-2.12)	1.68 (1.14-2.47)
7-9	1.46 (0.98-2.17)	2.82 (1.78-4.45)



potential to be dynamic taking into account changing patient, disease and treatment characteristics

Example of how a survival model would work?

75 year old Mr. BD
Hx of Type II diabetes
Lives in the country-side

Year 1	Year 2
• Presented with a fracture • VRd X 8→Rd • No hospital/ED visits • Active and continues to farm • Still has occasional pain at the site of the previous fracture	• Recent admission - pneumonia • Unable to participate in the same farming activities • Patient had 4 severe symptoms (pain, lack of energy, poor overall well-being and depression)
Probability of surviving another 1-yr 91.3 %	**Probability of surviving another 1-yr 83.5%**

Summary

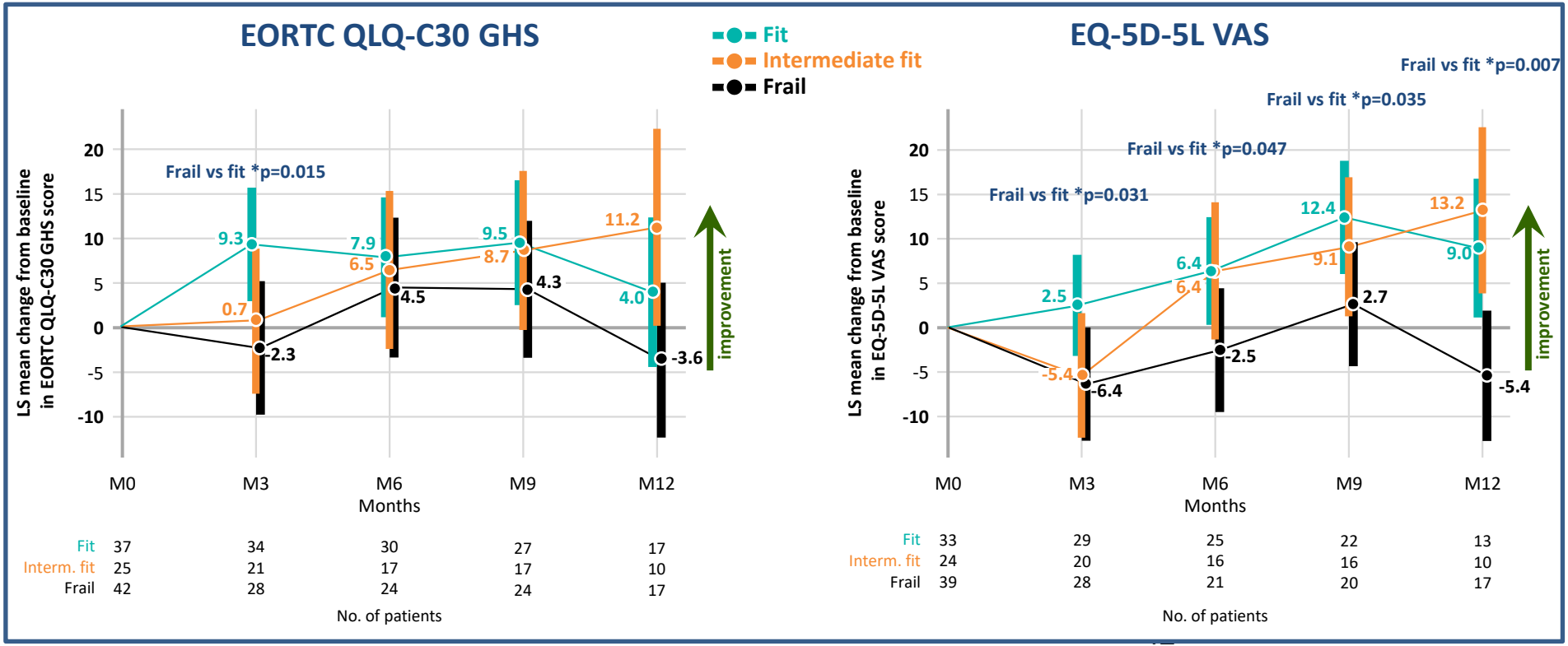
Prognostic Score Development:

- We developed a prognostic score incorporating patient reported outcomes
- This prognostic score has the potential to be dynamic taking into account changing patient, disease and treatment characteristics
- This tool could be used for conversations and shared decision making among patients with MM and their health care teams

Challenges for a frail patient

- Age and life expectancy → ***identify frail patients***
- Risk of toxicity and toxic deaths →***less intensive treatments***
- Weakened immune system and increased risk of infections →***prophylaxis***
- Social barriers →***patient preference and convenience***
- Quality of life →***treatment goals***
- Choice/selection of the appropriate treatment → ***personalized approach***

Quality of life (QoL) in frail patients



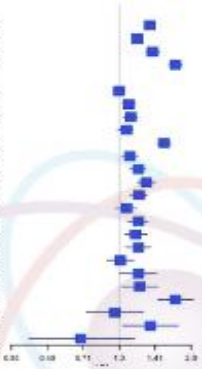
Frail patients show a **longlasting relatively lower QoL compared to fit patients.**

IMWG, International Myeloma Working Group; QoL, quality of life; GHS, GHS, Global Health Status; EORTC, European Organization for Research and Treatment of Cancer; Interm., intermediate; M, months.

Myeloma related symptoms and co-morbidities impacting quality of life

Comorbidities

	No.	HR	95% CI
Number of Comorbidities			
None	8,252	1.00	
One or more	7,404	1.34	1.29-1.40
One	3,355	1.19	1.14-1.25
Two	1,922	1.38	1.30-1.47
Three or more	2,126	1.72	1.62-1.83
Comorbidities			
Hypertension	2,793	1.00	0.95-1.06
Arrhythmia	1,551	1.10	1.03-1.17
Cancer	1,544	1.12	1.05-1.19
Chronic ischeemic heart disease	1,254	1.07	0.99-1.16
Heart failure	1,262	1.54	1.44-1.66
Diabetes mellitus	1,144	1.11	1.03-1.20
Cerebrovescular disease	1,055	1.20	1.11-1.29
Psychological disease	832	1.30	1.19-1.41
Chronic lung disease	823	1.21	1.11-1.31
Endocrine disease	673	1.07	0.97-1.18
Peptic Ulcer	518	1.20	1.09-1.32
Neurological disease	473	1.17	1.06-1.31
Peripheral vascular disease	381	1.20	1.07-1.35
Rheumatological disease	374	1.01	0.89-1.15
Chronic kidney disease	184	1.20	1.00-1.43
Liver disease	181	1.22	1.03-1.45
Dementia	149	1.72	1.45-2.04
Obesity	103	0.96	0.73-1.26
Inflammatory bowel disease	83	1.35	1.04-1.76
Pancreatic disease	29	0.69	0.42-1.16



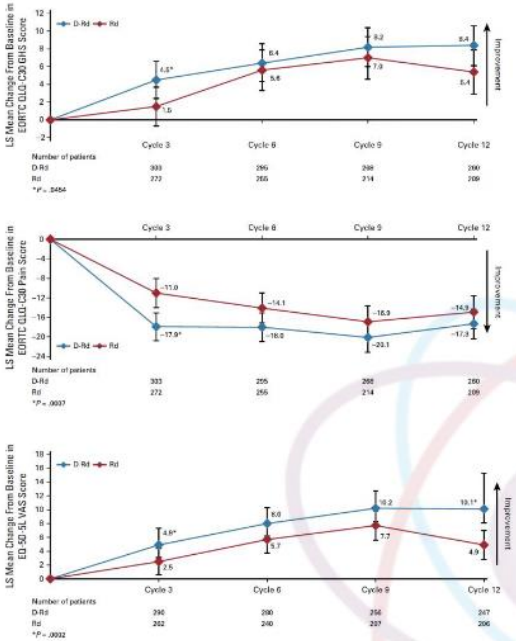
Common Characteristics

- Bone pain (often affecting the back)
- Malaise
- Anemia
- Renal failure
- Hypercalcemia
- Bone disease
- Bone marrow infiltration

International Myeloma Society

Eur J Haematol. 2021 Jun;106(6):774-782.

Health-Related Quality of Life in the Phase III MAIA Trial (DRd vs Rd)



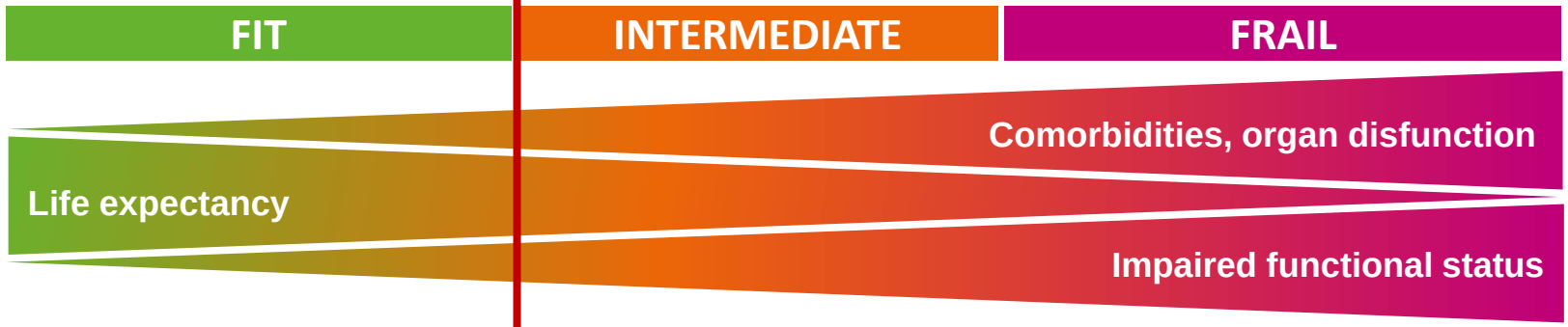
PRO	Improvement			Worsening		
	Rd	D-Rd	OR[a] (95% CI)	Rd	D-Rd	OR[a] (95% CI)
EQ-5D-5L						
VAS	50.4	54.3	1.17 (0.88 to 1.56)	42.8	44.8	1.09 (0.81 to 1.45)
Global health status/QoL						
Global health status	48.5	52.7	1.18 (0.89 to 1.58)	40.9	43.8	1.12 (0.84 to 1.50)
Functional scales						
Physical functioning	40.9	49.7	1.43 (1.07 to 1.91)	39.6	38.6	0.96 (0.71 to 1.29)
Role functioning	45.5	52.7	1.33 (1.00 to 1.78)	49.1	52.2	1.13 (0.85 to 1.51)
Emotional functioning	42.5	47.0	1.20 (0.90 to 1.60)	35.5	36.1	1.03 (0.76 to 1.39)
Cognitive functioning	34.4	36.1	1.08 (0.80 to 1.46)	49.6	57.3	1.37 (1.02 to 1.83)
Social functioning	38.5	45.4	1.33 (0.99 to 1.78)	50.7	51.1	1.02 (0.76 to 1.36)
Symptom scales						
Fatigue	52.0	62.2	1.52 (1.13 to 2.04)	57.2	60.3	1.14 (0.85 to 1.53)
Nausea and vomiting	18.2	18.8	1.04 (0.72 to 1.51)	34.4	38.6	1.20 (0.89 to 1.62)
Pain	59.6	65.2	1.27 (0.94 to 1.71)	40.7	37.8	0.89 (0.66 to 1.19)

Abbreviations: D-Rd, daratumumab, lenalidomide, and dexamethasone; EQ-5D-5L, EuroQol 5-dimensional descriptive system; OR, odds ratio; QoL, quality of life; PRO, patient-reported outcome; Rd, lenalidomide and dexamethasone; VAS, visual analog scale.

[a]Improvement or worsening defined as increase or decrease in score equal to at least half of standard deviation from baseline values, where standard deviation is calculated from the scores at baseline combining both treatment groups. OR based on the Cochran-Mantel-Haenszel estimate. ORs for improvement > 1 and ORs for worsening < 1 favor D-Rd.

J Clin Oncol. 2021. PMID: 33326255

Treatment goals in elderly MM patients



	Deep remission	Balance efficacy/safety	Do not harm
Goal	CR/MRD-negativity	Good response	QoL
Priority	Efficacy	Combination of efficacy/safety	Low toxicity

CR, complete response; MM, multiple myloma; MRD, minimal residual disease; QoL, quality of life.
Image reproduced with permission: Scale by Larea from Noun Project.
Personal communication.

Challenges for a frail patient

- Age and life expectancy → ***identify frail patients***
- Risk of toxicity and toxic deaths →***less intensive treatments***
- Weakened immune system and increased risk of infections →***prophylaxis***
- Social barriers →***patient preference and convenience***
- Quality of life →***treatment goals***
- Select the appropriate treatment → ***personalized approach***

Frailty

- VRd-lite and DRd-lite
- Limited Duration
  Stopping Dex in one year
  Stopping Daratumumab in standard risk frail patients
- Too frail for triplets

Duration of Therapy

- Long term toxicity
  - Second malignancies
  - Infections
  - Cytopenias
  - Diarrhea
  - Cramps
  - Cost
  - QOL

- **RCTs**
  - **2 years vs Indefinite**
  - **MRD directed**

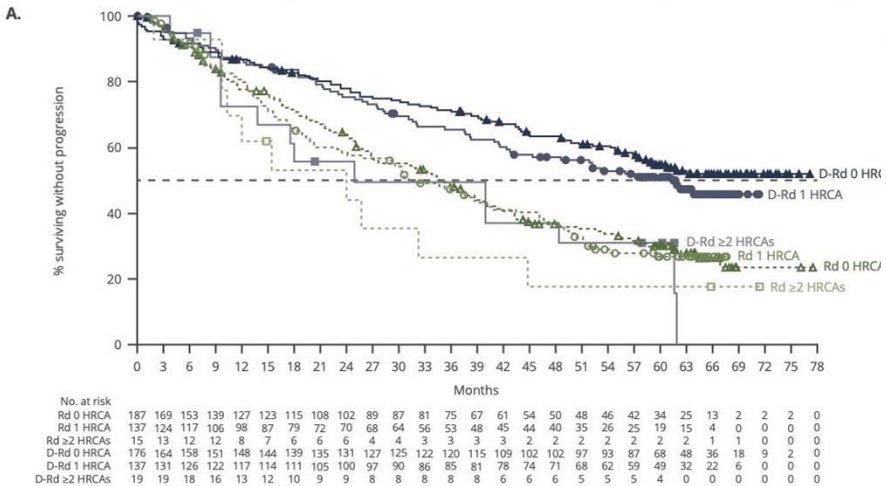
- **Curative Trials**

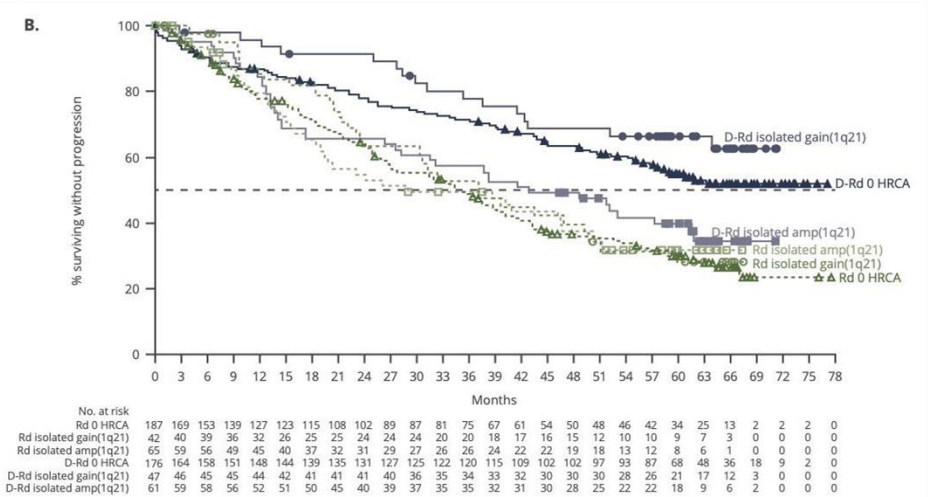
Rajkumar SV. 2023

Continuous or fixed-duration treatment
MAIA cytogenetic risk subgroups

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)





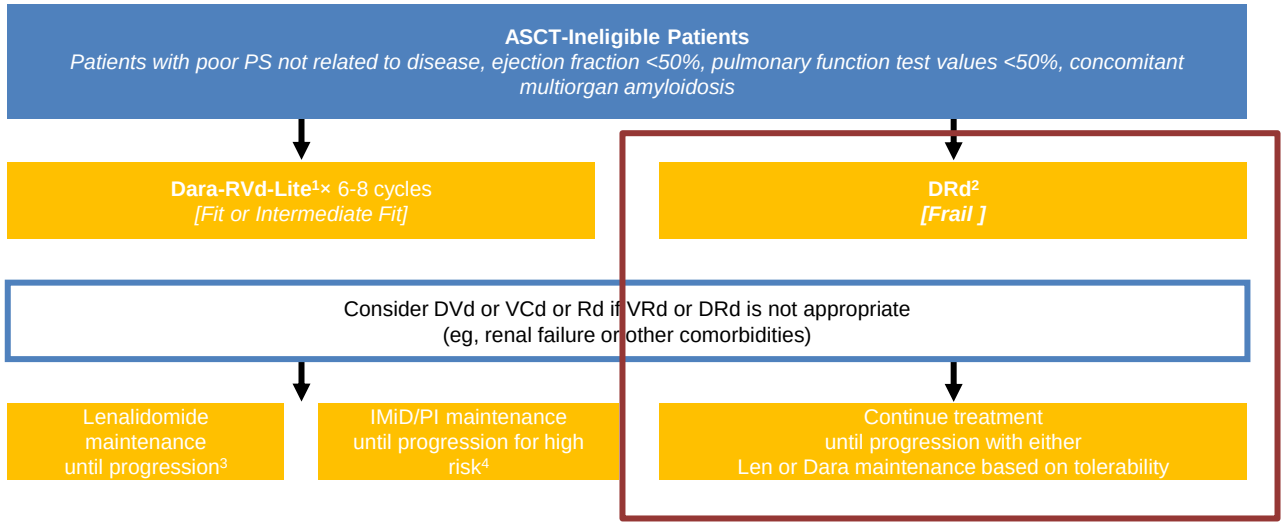
Newly Diagnosed MM: continuous treatment in very high risk.

Can we de-intensify/stop treatment in low-risk?

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

Moreau P et al. ASH 2022;abstract 3245 (poster presentation)

MSK Approach to Transplant Ineligible NDMM (? 2024)



- DRd, daratumumab, lenalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; VRd-Lite, modified VRd regimen.
- Adjust dosing of lenalidomide based on renal function. Consider empiric age-adjusted dose reductions for all regimens, as needed.[4]
- 1. O'Donnell. Br J Haematol. 2018;182:222. 2. Facon. ASH 2018. Abstr LBA-2. 3. Larocca. ASH 2018. Abstr 305. 4.Usmani. *Lancet Haematol*. 2021 Jan;8(1):e45-e54.

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

Managing the older, frail patient with multiple comorbidities

Salomon MANIER
Professor of Hematology, Lille University Hospital

September 2023

- Frailty assessment is an important considerations when treating older patients with MM
- Frail patients have shorter PFS and OS likely due to more AEs and treatment discontinuation
- Treatment objectives and strategies should be different for fit and frail NTE patients
  - Improving MRD negativity rate for fit patients
  - Limiting toxicity for frail patients
- Multiple tools, not all easy to apply in clinical practice and with often a high weigh on age
- Dexamethasone sparing regimens seem to be effective to limit the risk of infections
- Future role of new generation immunotherapies in frail patients need to be explored

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Cancer Heterogeneity, Plasticity and Resistance to Therapies

REAL-MM STUDY

The Real MM Trial (NCT03829371) was funded by the Italian Medicines Agency AIFA - Independent Research.

Newly diagnosed MM with symptomatic disease and ineligible for transplant

Randomization 1:1

Stratification for:
- Cytogenetic risk
- Frailty

Dara-VMP

Daratumumab 16 mg/Kg D1,8,15,22,29,36 cycle 1;
D1, 22 cycle 2-9; every 28 days cycle 10+
Bortezomib 1.3 mg/m^2 D1,4,8,11,22,25,29,32 cycle 1-4;
1.3 mg/m^2 D1,8,22,29 cycle 5-9
Melphalan 9 mg/m^2 D1-4
Prednisone 60 mg/ m^2 D1,8,15,22

Up to nine 42-day VMP cycles Dara until PD, death or unacceptable toxicity

Dara-Rd

Daratumumab 16 mg/Kg D1,8,15,22 cycle 1-2;
D1, 15 cycle 3-6; every 28 days cycle 7+
Lenalidomide 25 mg D1-21
Dexamethasone 40 mg/day* D1,8,15,22
* 20 mg/day D1,8,15,22 for patients ≥75 years

Until PD, death, or unacceptable toxicity

- **Primary objective: PFS**
- **Additional secondary objective: MRD by NGF at 6th-12th-24th-36th-48th-60th months**

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