Nessun paziente viene lasciato indietro: la terapia del mieloma multiplo in popolazioni speciali di pazienti, Il paziente di età pari o superiore a 80 anni

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HIGHLIGHTS IN EMATOLOGIA
TREVISO, 1-2 DICEMBRE 2023

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Bristol						x	
Jannsen						x	
Menarini						x	
Amgen						x	
Sanofi						x	
Oncopeptide						x	

Multiple myeloma is mainly a disease of the elderly, with the majority of cases being diagnosed in patients older than 65 years of age[1]

Approximately 2/3 of patients are **>65 years old** at initial diagnosis and 1/3 are **>75 years old**[1]

The median age at diagnosis is **70 years old**[1]

As incidence increases with age, the incidence of multiple myeloma is expected to increase by 77% by 2030 in patients over 65 years of age **due to the aging population**[2]

Real-world considerations become increasingly important in older and frailer MM patients due to **discrepancies** between the true disease demographics versus clinical trial **demographics** and real-world versus clinical-trial **efficacy**[3,4]

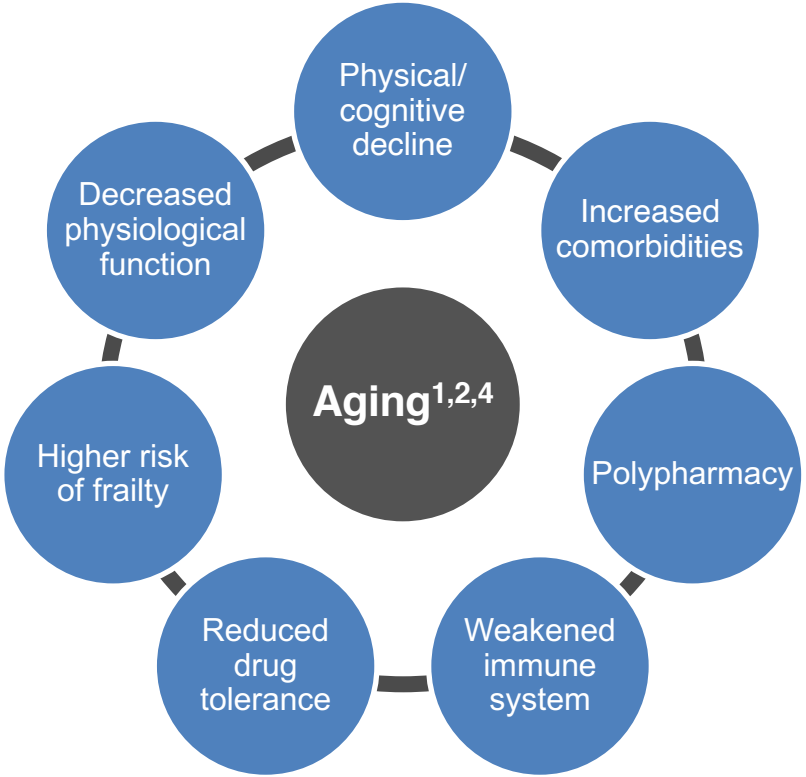
Patients treated with the MAIA regimen are experiencing **longer 1L remission** and are thus **older when they relapse** and initiate 2L treatment[5]

Relapse may be **more devastating in elderly** patients than in younger patients, considering many elderly patients are **not fit enough to receive treatment upon relapse**[6]

1. Kaweme NM et al. *Front Med (Lausanne*). 2021;8:612696. doi:10.3389/fmed.2021.612696 **2.** Manapuram S, Hashmi H. *Cureus*. 2018;10(12):e3669. doi:10.7759/cureus.3669 **3.** Borad A et al. *J Oncol Pharm Pract*. 2020;26(6):1475-1481. **4.** Richardson PG et al. *Blood Cancer J*. 2018;8(11):109. doi:10.1038/s41408-018-0141-0 **5.** Facon T et al. *N Engl J Med.* 2019;380(22):2104-2115. **6.** Bonello F et al. *Cancers (Basel)*. 2020;12(11):3106. doi:10.3390/cancers12113106

Elderly patients with multiple myeloma present with variable disease characteristics[1,2]

The clinical manifestation of MM is frequently nonspecific in elderly patients, causing delays in diagnosis[1,3]



1. Kaweme NM et al. *Front Med (Lausanne*). 2021;8:612696. doi:10.3389/fmed.2021.612696 **2.** Bonello F et al. *Cancers (Basel)*. 2020;12(11):3106. doi:10.3390/cancers12113106 **3.** Zanwar S et al. *Curr Hematol Malig Rep*. 2019;14(2):70-82. **4.** Hilmer SN et al. *Fundam Clin Pharmacol*. 2007;21(3):217-230.

Elderly patients often have compromised immune systems, making them more susceptible to infections and impacting their ability to tolerate certain treatments[1-3]

There are marked changes in both innate and adaptive immunity associated with age.[1]

These changes are thought to contribute to the increased frequency of some infections among the elderly population.[1]

Innate[1]	Adaptive[1,2]
• Impaired neutrophil migration • Slower wound healing • Changes in: – Macrophage phagocytosis – Antibacterial effector function – Cytokine production	• Thymic involution • T-cell senescence • Reduced naïve T-cell output • Mitochondrial dysfunction • Genetic and epigenetic modification of T cells • Reduced TCR diversity

Progressive immunodeficiency due to alterations in immune responses makes the elderly population vulnerable to a host of potential infections[1,2]

1. Kline KA, Bowdish DME. *Curr Opin Microbiol.* 2016;29:63-67. **2.** Mittelbrunn M, Kroemer G. *Nat Immunol*. 2021;22(6):687-698. **3.** Kaweme NM et al. *Front Med (Lausanne)*. 2021;8:612696. doi:10.3389/fmed.2021.612696

HETEROGENEITY OF THE AGING POPULATION

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

Intermediate fit

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

Age alone is not sufficient to identify frailty status or guide disease management—all patient characteristics must be taken into account[1-3]

The inability of elderly patients to tolerate treatment toxicities translates into morbidity, mortality, and inadequate treatment exposure[1]

Treatment-related AEs impact survival outcomes in MM patients[2]

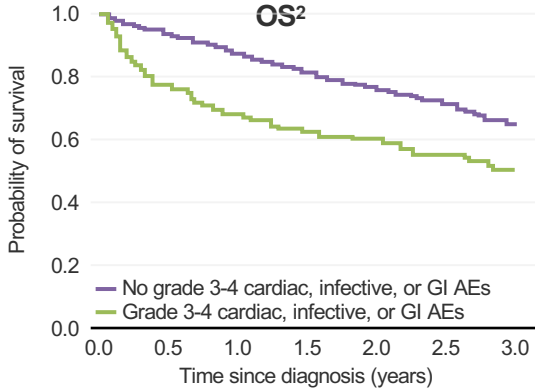
- Despite treatment optimization, **treatment discontinuation** due to AEs still occurs in about **10-15% of elderly patients**[1]

Approximately **10% of patients ≥80** years old experience **deaths** related to **treatment toxicity**[1]

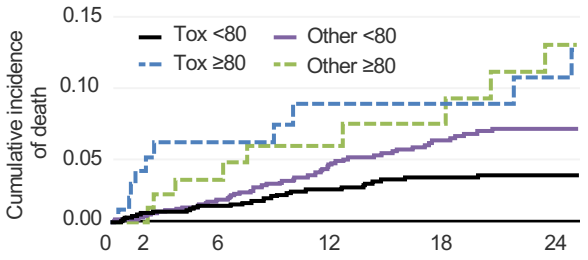
- Death due to treatment toxicity occurs approximately four times more often in patients in their 80s than it does in younger patients[3]

Frailty tools and thorough assessment of disease and patient characteristics are necessary to distinguish which patients can tolerate more **intense treatment** regimens versus those that require a **gentler treatment** approach[1,4]

Impact of treatment-related AEs on OS[2]



Death due to treatment toxicity versus other causes according to age[3]



- AE, adverse vent; GI, gastrointestinal; MM, multiple myeloma, OS, overall survival; tox, toxicity.

1. Bonello F et al. *Cancers (Basel)*. 2020;12(11):3106. doi:10.3390/cancers12113106 **2.** Bringhen S et al. *Haematologica*. 2013;98(6):980-987. **3.** Bringhen S et al. *Crit Rev Oncol Hematol*.2018;130:27-35. **4.** Kaweme NM et al. *Front Med (Lausanne)*. 2021;8:612696. doi:10.3389/fmed.2021.612696

YC

Tools for geriatric assessments in MM patients

IMWG Frailty score

Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 ys	1	-	0
	Age 75-80 ys	1.13 (0.76-1.69)	0.549	1
	Age >80 ys	2.40 (1.56-3.71)	<0.001	2
CHARLSON Index	Charlson ≤1	1	-	0
	Charlson ≥2	1.37 (0.92-2.05)	0.125	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.67 (1.08-2.56)	0.02	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.43 (0.96-2.14)	0.078	1

ADDITIVE TOTAL SCORE	PATIENT STATUS
0	FIT
1	INTERMEDIATE
≥2	FRAIL

ADL, Activities of Daily Living; CCI, Charlson Comorbidity Index;
CI, confidence intervals; CRP, C-reactive protein;
CT, computerized tomography;
ECOG, Eastern Cooperative Oncology Group;
EORTC, European Organisation for Research and Treatment of Cancer;
HR, hazard ratio; IADL, Instrumental Activities of Daily Living;
IMWG, International Myeloma Working Group;
ISS, international staging system; MRP, Myeloma Risk Profile;
NTproBNP, N-terminal pro-brain natriuretic peptide;
OS, overall survival; PFS, progression-free survival; QoL, quality of life; R-MCI, revised Myeloma Comorbidity Index;
WHO, World Health Organisation

INCLUDING PROGNOSTIC FEATURES

R-MCI SCORE
- Age
- Comorbidities
  - Renal function
  - Pulmonary function
- Frailty evaluation
- Karnofsky performance status
- Cytogenetics

Fit score ≤3 | Intermediate fit score 4-6 | Frail score >6

MRP score
- Age
- WHO performance status
- ISS stage
- Circulating CRP levels

Low risk | Medium risk | High risk

INCLUDING OBJECTIVE PARAMETERS

MAYO CLINIC SCORE
- Age
- ECOG performance status
- Circulating NTproBNP levels

Stage I score 0 | Stage II score 1 | Stage III score 2 | Stage IV score 3

EVALUATION OF SARCOPENIA
- Muscle mass: CT 3rd lumbar vertebra area
- Muscle function: grip strength
- Physical performance: gait speed, etc..

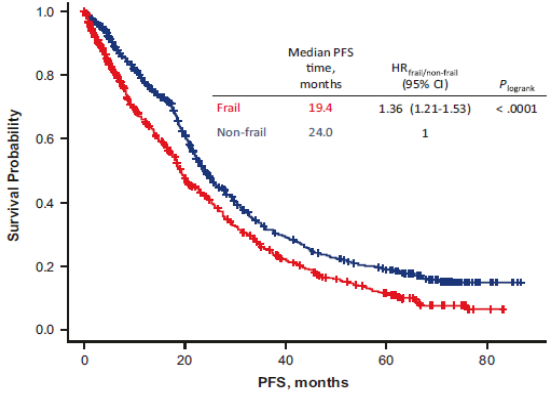
SENESCENCE BIOMARKERS

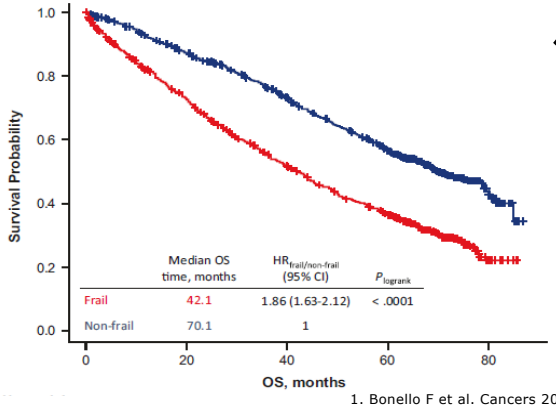
SIMPLIFIED ASSESSMENTS

SIMPLIFIED FRAILTY SCORE
- Age
- Comorbidities
  - CCI
- ECOG Performance Status

Non-frail score 0-1 | Frail score ≥2

QUALITY-OF-LIFE QUESTIONNAIRES
- Patient-reported functional status
  - EORTC QoL questionnaire C30





1. Bonello F et al. Cancers 2020;12(11):3106
2. Facon T et al. Leukemia 2020;34(1):224–233
3. Adapted from Palumbo A et al. Blood 2015;125(13):2068–2074

Fit no-transplant eligible (NTE) multiple myeloma patients

Fit Patients

Age ≤ 75 years

No significant comorbidities (CCI ≤ 1)

Functionally active and independent (ADL > 4; IADL > 5)

Goal of treatment
Deep remission
CR/MRD-negativity

Priority
Efficacy

Candidate to full dose treatment

CCI: Charlson Comorbidity Index; ADL: Activity of Daily Living; IADL: Instrumental Activity of Daily Living

Palumbo A, et al, Blood 2015;125(13):2068-74;
Larocca A, Palumbo A. J Clin Oncol 2016;34(30):3600-3604

No-fit NTE multiple myeloma patients

Intermediate-fit patients

Age 76 to 80 years

or ADL ≤ 4 or IADL ≤ 5 or CCI ≥ 2

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

Goal of treatment
Good response

Priority
Balance efficacy-safety

Candidate to adjusted-treatment

Frail patients

Age > 80 years regardless of ADL, IADL, or CCI;

age 76 to 80 years and either ADL ≤ 4, IADL ≤ 5, or CC ≥ 2; or

age ≤ 75 years and at least two: ADL ≤ 4, IADL ≤ 5, and CC ≥ 2

Need help for household tasks, partially for self-care
Dependent on other people
Higher treatment discontinuation

Goal of treatment
Balance efficacy/QoL

Priority
Low toxicity

Candidate to tailored-treatment

CCI: Charlson Comorbidity Index; ADL: Activity of Daily Living; IADL: Instrumental Activity of Daily Living

Palumbo A, et al, Blood 2015;125(13):2068-74;
Larocca A, Palumbo A. J Clin Oncol 2016;34(30):3600-3604

Treatment strategies in NTE MM patients

- Tailored treatment based on frailty status?
- Treatment sequencing?
- How to improve the treatment strategy of NDMM?

Treatment strategies in NTE MM patients

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Fit

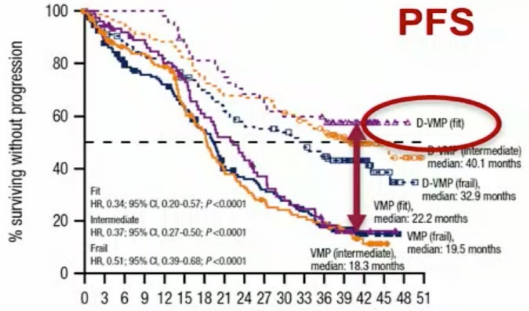
Intermediate- Fit

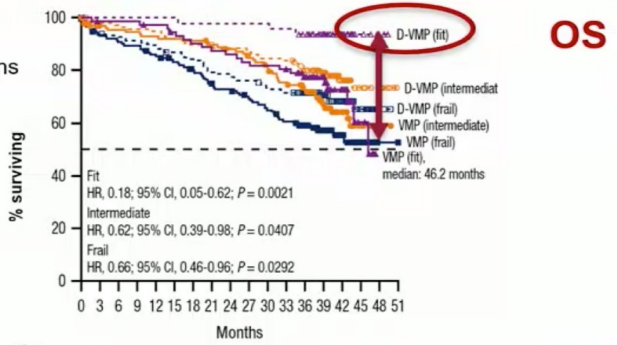
Frail

Fit multiple myeloma patients

ALCYONE

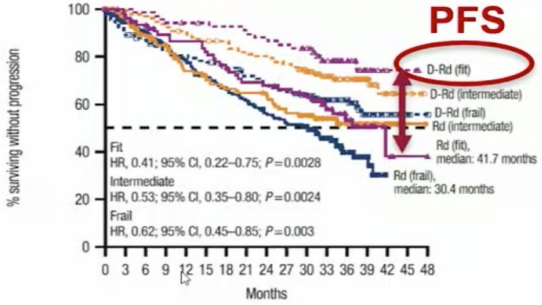
Median follow-up 40 months

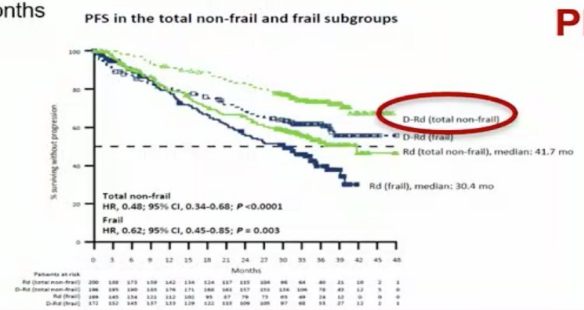




MAIA

Median follow-up 36.4 months





Adding daratumumab substantially improved the outcome, in particular of fit patients

Mateos MV et al, Clin Lymphoma Myeloma Leuk 2021; Facon et al, Leukemia 2022

Fit multiple myeloma patients

Modified VRd (VRd-lite)

Phase 2 Study

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)

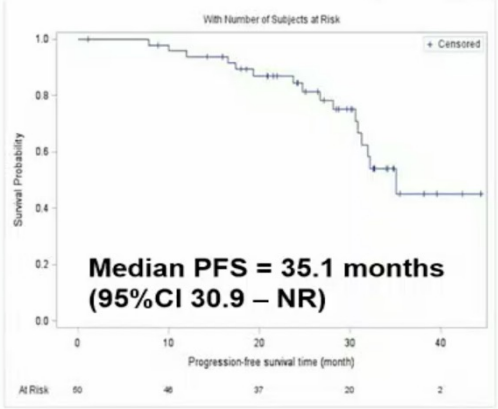
↓

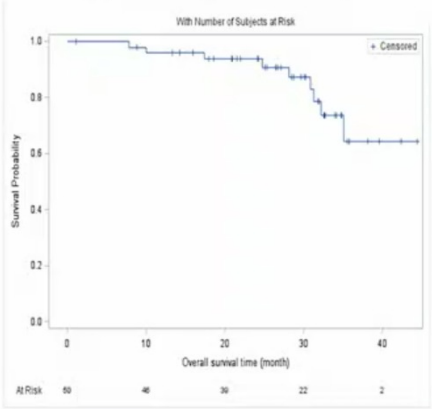
Consolidation (cycles 10-15)
Repeat q28 days × 6 cycles

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.

Median age 73 years (range 65–91)
ECOG PS 0 in 50%, 1 in 36%, and 2 in 14 % of patients.
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 was well-tolerated and highly effective in TNE patients with robust PFS and OS

V, bortezomib; R, lenalidomide; d, dexamethasone.

O'Donnell et al, Br J Haematol 2018;182:222

Intermediate-fit multiple myeloma patients

Dose/Schedule-Adjusted Rd-R vs continuous Rd

RV-MM-PI-0752 Phase III Randomized Study

Randomization

Rd-R

Rd INDUCTION
9 cycles
R: 25 mg/day PO days 1-21
d: 20 mg PO once weekly

R MAINTENANCE
until PD/ intolerance
R: 10 mg/day PO days 1-21

Rd

CONTINUOUS Rd
until PD/ intolerance
R: 25 mg/day PO days 1-21
d: 20 mg PO once weekly

Steroid sparing strategy

Larocca et al, Blood 2021, 137(22):3027-3036

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

Antibiotic and -viral prophylaxis: Cotrimoxazole 480 mg/day, Valaciclovir 500 mg twice daily
Vaccinations according to local policy

Less toxic drugs and adjusted dosing

Zweegman et al., ASH 2021

Intermediate-fit multiple myeloma patients

	RV-MM-PI-0752 Rd-R 101 patients	HOVON 143 Dara-Ixa-Dex 65 patients	MAIA Dara-Rd 128 patients
Median age	75	76	72 ↓
≥ 75 years	48%	57%	27.3% ↓
≥80 years	Excluded	Excluded	4.7%
ECOG PS			
0-1	85%	81%	100% ↑
2	11%	9%	0
> 2	0	5%	Excluded
Creatinine clearance			
30-60 ml/min	22% (30-50 ml/min)		34.4%
< 30 ml/min	5%		0
	IMWG frailty score	IMWG frailty score	Frailty assessed retrospectively using age, CCI (review medical history), ECOG PS
CCI ≥2	23%	29%	
ADL ≤4	9%	0%	
IADL ≤5	21%	14%	

Need a uniform definition of frailty status

Facon T et al, Leukemia 2022

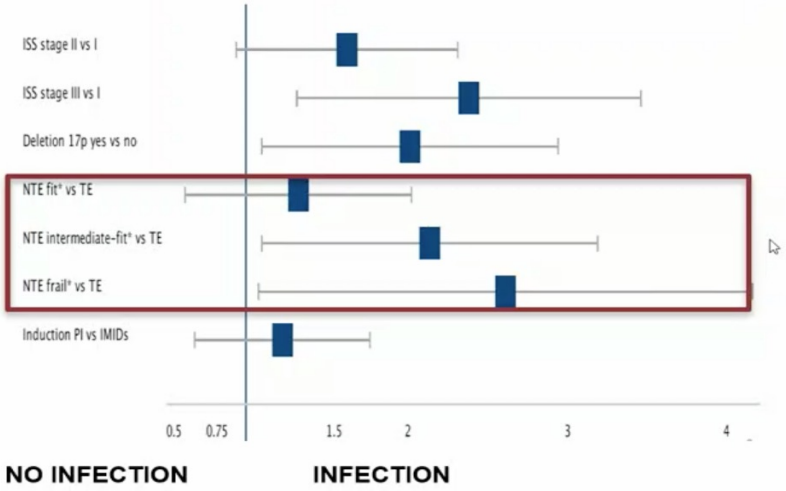
Frail multiple myeloma patients

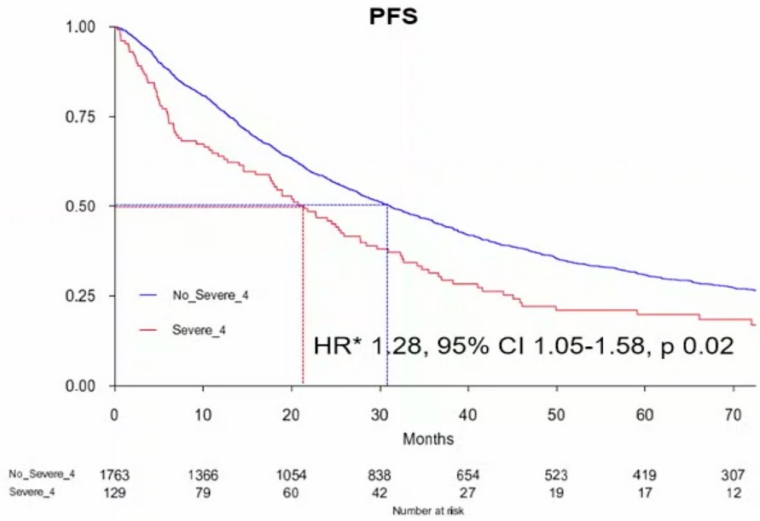
	RV-MM-PI-0752 Rd-R 101 patients	HOVON 143 Dara-Ixa-Dex 65 patients	MAIA Dara-Rd 128 patients	MAIA Dara-Rd FRAIL 172 patients
ORR	78%	71%	96.9%	98% ↑
PFS	20.2 mo	17.4 mo	Not reached	Not reached ↑
DOT	17 mo	NA	33.2 mo	31.1 mo ↑
Infections ≥G3	10%	9%	35.9%	41.7% ↑
Toxic deaths	5%	8% (non rel mortality)	4.7%	11.9% ↑
Discontinuation for PD	34%	29%*	19.5%	18.6%
Discontinuation for AE	18%	6%*	7%	9.9%
Discontinuation for non compliance with study	NA	4.6%	3.9%	4.7%
	52%	39.6%	30.4%	33%
Median f-up	*37 mo*	*18 mo*	*36.4 mo*	*36.4 mo*

One third of intermediate-fit and frail MM patients discontinued therapy

Facon T et al, Leukemia 2022

Managing toxicity in frail patients: infections





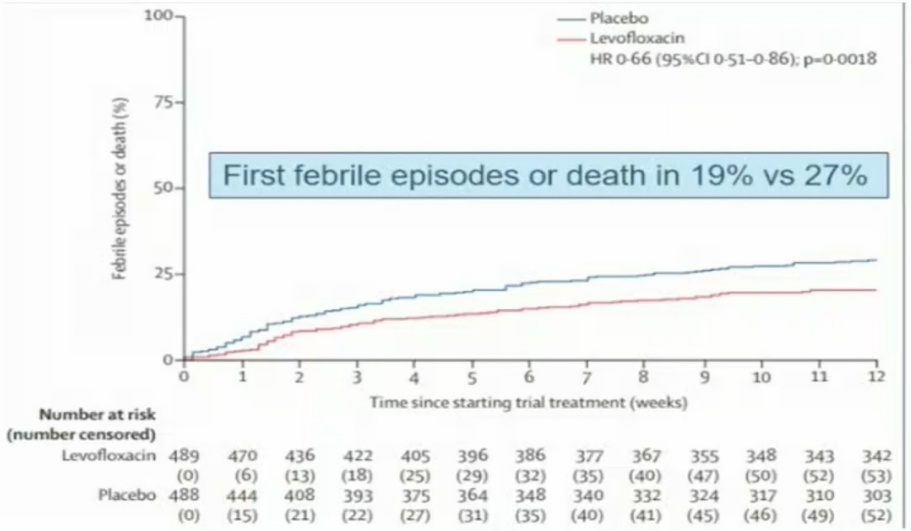
The risk of early severe infections was higher in intermediate-fit and frail patients and negatively affects outcome

Bonello F et al, ASH 2020

Antibiotic prophylaxis in newly diagnosed MM

TEAMM phase 3 trial

N= 977 NDMM. Oral levofloxacin 500 mg vs placebo during the first 12 weeks of therapy.



Prophylactic levofloxacin significantly reduced febrile episodes and deaths compared with placebo

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

Frailty-adjusted treatments

IFM 2017-03

340 patients (frail)

Primary endpoint - PFS

LT Follow-up

Active Treatment + PFS Follow-up Phase

RANDOMIZATION 1:2

2 — Arm A **R-DaraSC**
LEN + Dara SC continuously:
LENALIDOMIDE
25mg D1-21/28
DARATUMUMAB SC
1800mg SC Q1Wk for 8 weeks
1800mg SC Q2Wk for 16 weeks
1800mg SC Q4Wk thereafter

1 — Arm B **Rd**
LEN + Lo-DEX continuously:
LENALIDOMIDE
25mg D1-21/28
Lo-DEXAMETHASONE
20mg D1, 8, 15 & 22/28

PD or Unacceptable Toxicity

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)

Steroid sparing regimen

UK-MRA FitNEss trial

FiTNEss
UK-MRA Myeloma XIV

Elderly +/- Frail patients (n=740)

Non-frailty adjusted induction → IxRd

Frailty Index-adjusted induction
- Fit → IxRd No Dose Reduction
- Intermediate → IxRd Dose Reduction 1
- Frail → IxRd Dose Reduction 2

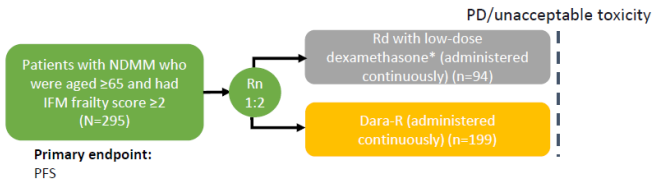
Maintenance: ⓟR vs IxR

Concept of frailty-adjusted dosing

www.clincaltrials.gov identifier: NCT03993912. Fitness trial - NCT03720041

Dexamethasone-sparing regimens have also been investigated to reduce toxicities in frail patients with NDMM[1]

IFM2017-03: Randomised Phase III trial evaluating dexamethasone-sparing dara-R vs Rd[1]



The IFM frailty score was used to determine eligibility for IFM 2017-03[1]

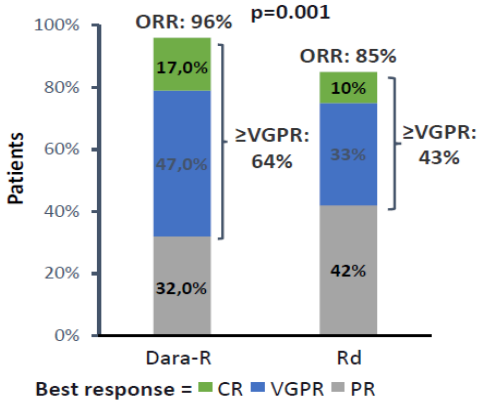
Safety summary[1]

Parameter, %	Dara-R (n=199)	Rd (n=94)
All grade ≥3 AEs	82	68
SAEs	55	63
Hematological AEs	55	26
Infections, n (%)	13	18
Discontinuations due to AEs	**14**	**16**

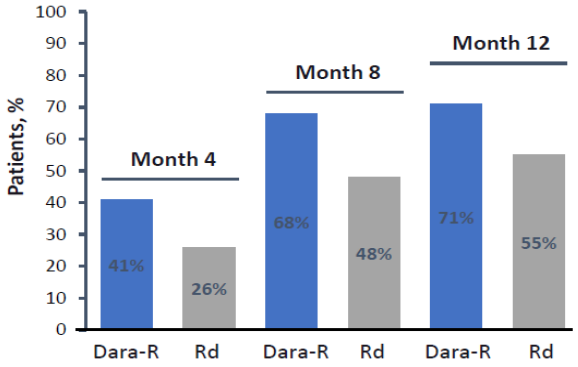
Similar frequencies of infections and AE-related treatment discontinuations with dara-R and Rd demonstrate the benefits of dexamethasone-sparing regiments in this population

*20 mg dexamethasone.
AE, adverse event; dara-R, daratumumab/lenalidomide; NDMM, newly-diagnosed multiple myeloma; PD, progressive disease; PFS, p
SAE, serious adverse event.
1. Manier J, et al. ASH 2022 (Abstract No. 569 – oral presentation).

Response results[1]



≥VGPR over time[1]



Manier S et al, ASH 2022

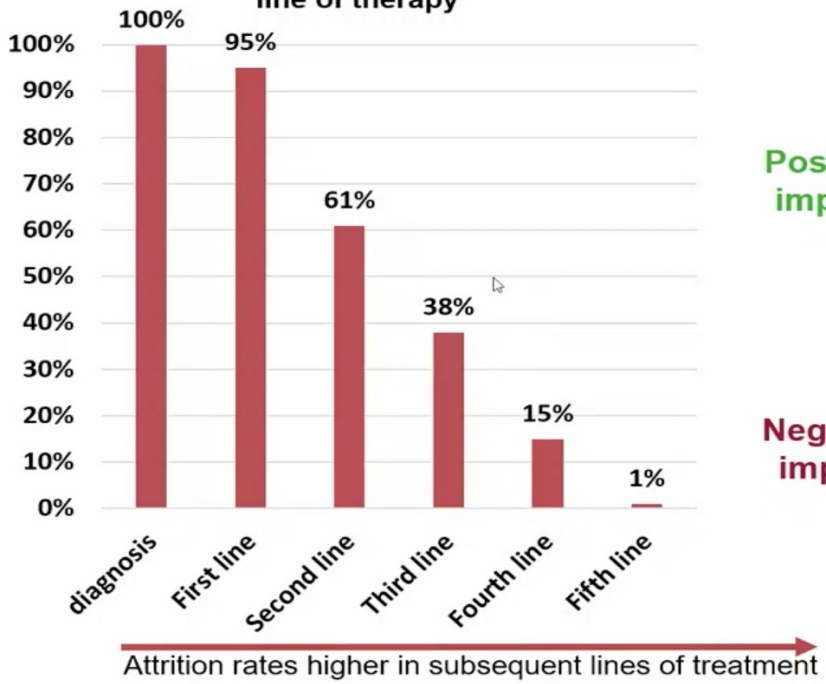
Treatment strategies in NTE MM patients

- Tailored treatment based on frailty status?
- Treatment sequencing?
- How to improve the treatment strategy of NDMM?

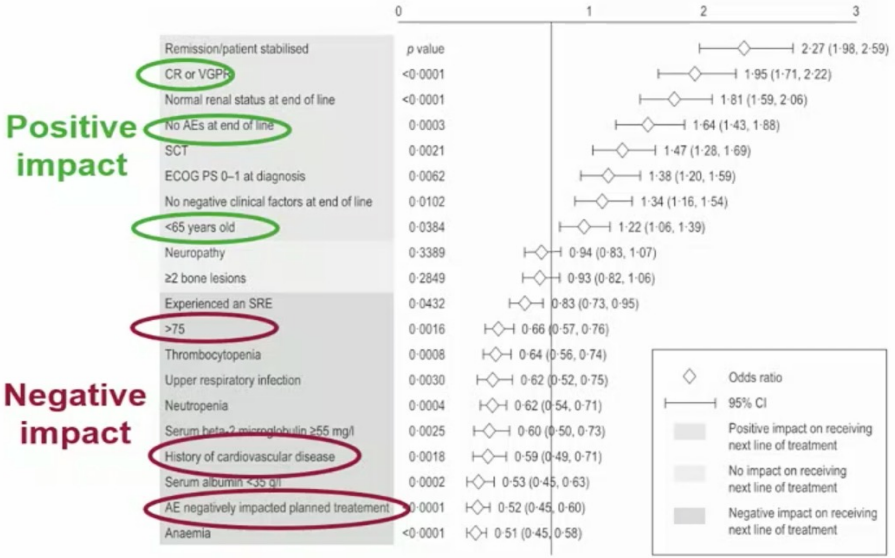
First line treatment

Real life population

Proportion of patients reaching each line of therapy



Relative probability of receiving a further line of therapy

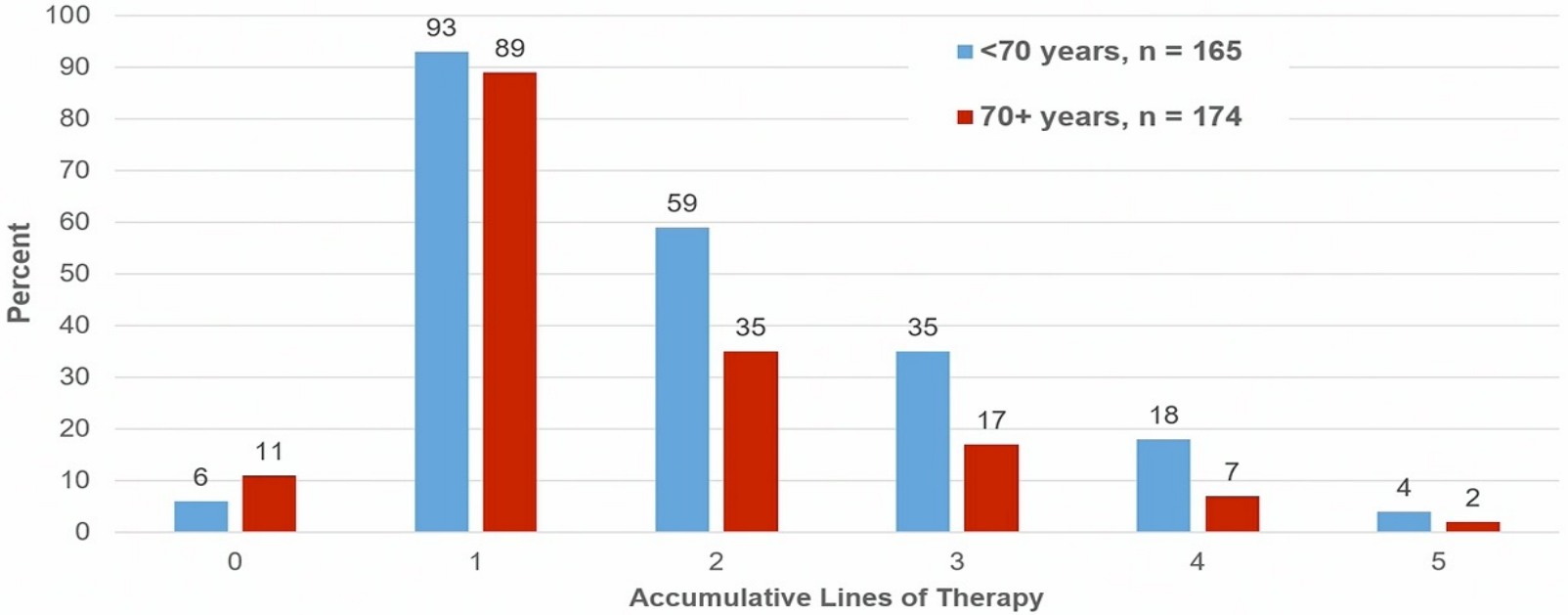


AEs, adverse events; CR, complete response; ECOG, European Cooperative Oncology Group; SCT, stem cell transplant; SRE, skeletal-related event; VGPR, very good partial response.

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

Accumulative lines of therapy received by age at diagnosis

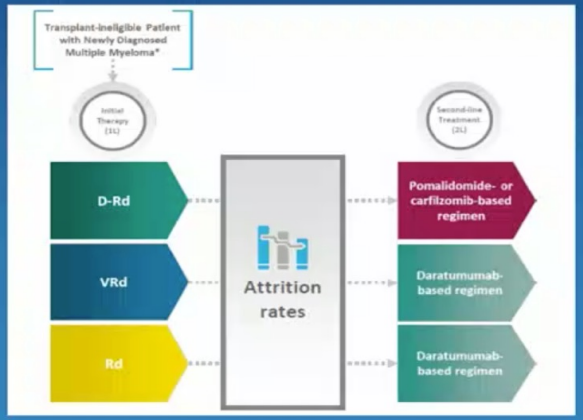
Myeloma & related diseases registry



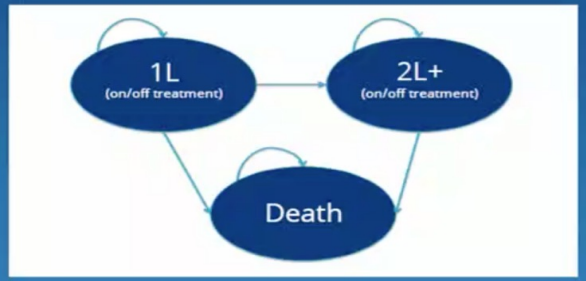
Courtesy of Dr A. Spencer

First-line Use of Dara-Rd compared with 2nd-line Dara-based regimens in TNE MM

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



- We used a simulation with 3 health states that represent different stages on the patient treatment journey

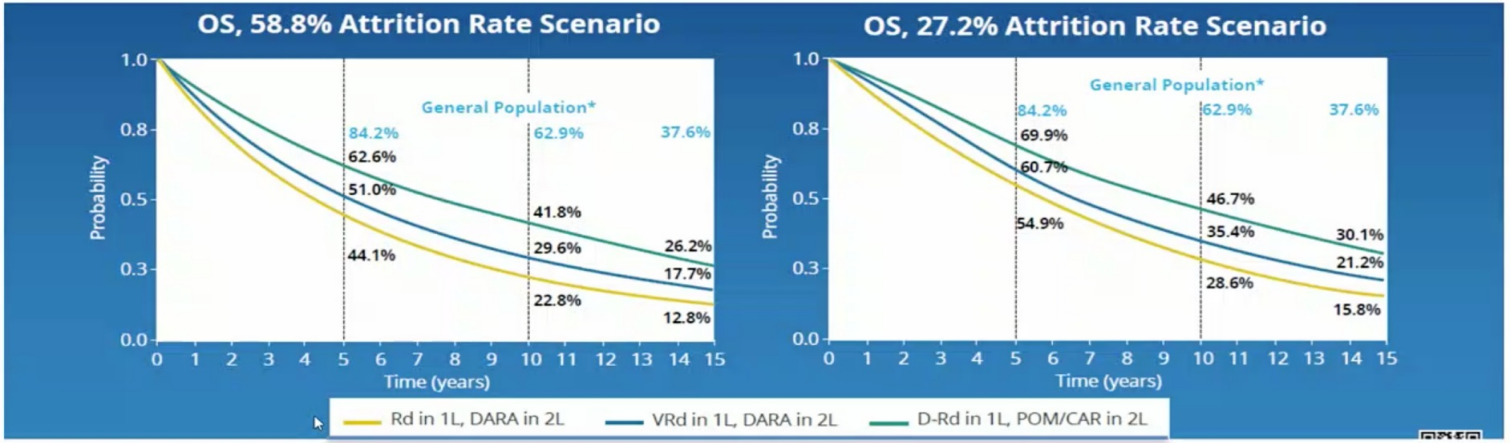


- Attrition rates from first- to second-line treatment were incorporated
- We evaluated median OS rates at 5, 10, and 15 years

*average age 74.1 years.
D-Rd, daratumumab, lenalidomide, and dexamethasone; OS, overall survival; Rd, lenalidomide and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone
Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

Fonseca R et al, ASH 2021, abs 118

First-line Use of Dara-Rd compared with 2nd-line Dara-based regimens in TNE MM



- D-Rd in 1L improved OS by 2.5 or 3.5 years compared with delaying DARA-based regimens until 2L after VRd or Rd, respectively.
- The probability of being alive at 5,10 years was higher with D-Rd than with VRd or Rd as initial therapy

Achieving the longest possible PFS in 1L drives OS outcomes

Fonseca R et al, ASH 2021, abs 118

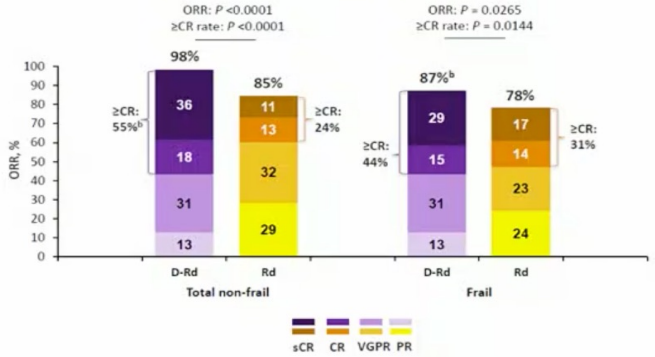
Treatment strategies in NTE MM patients

- Tailored treatment based on frailty status?
- Treatment sequencing?
- How to improve the treatment strategy of NDMM?

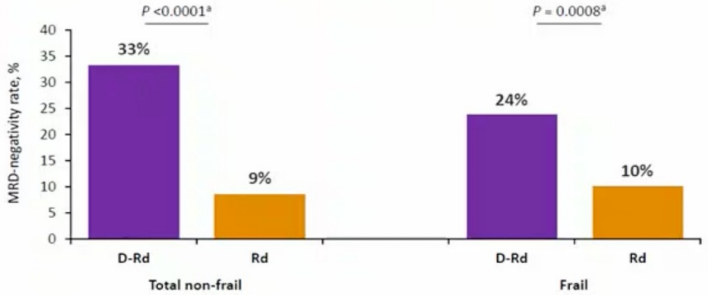
MAIA study: Outcomes by Frailty Subgroup

Clinical benefit of D-Rd in patients with transplant-ineligible NDMM enrolled in MAIA, regardless of frailty status

ORR and ≥CR rate



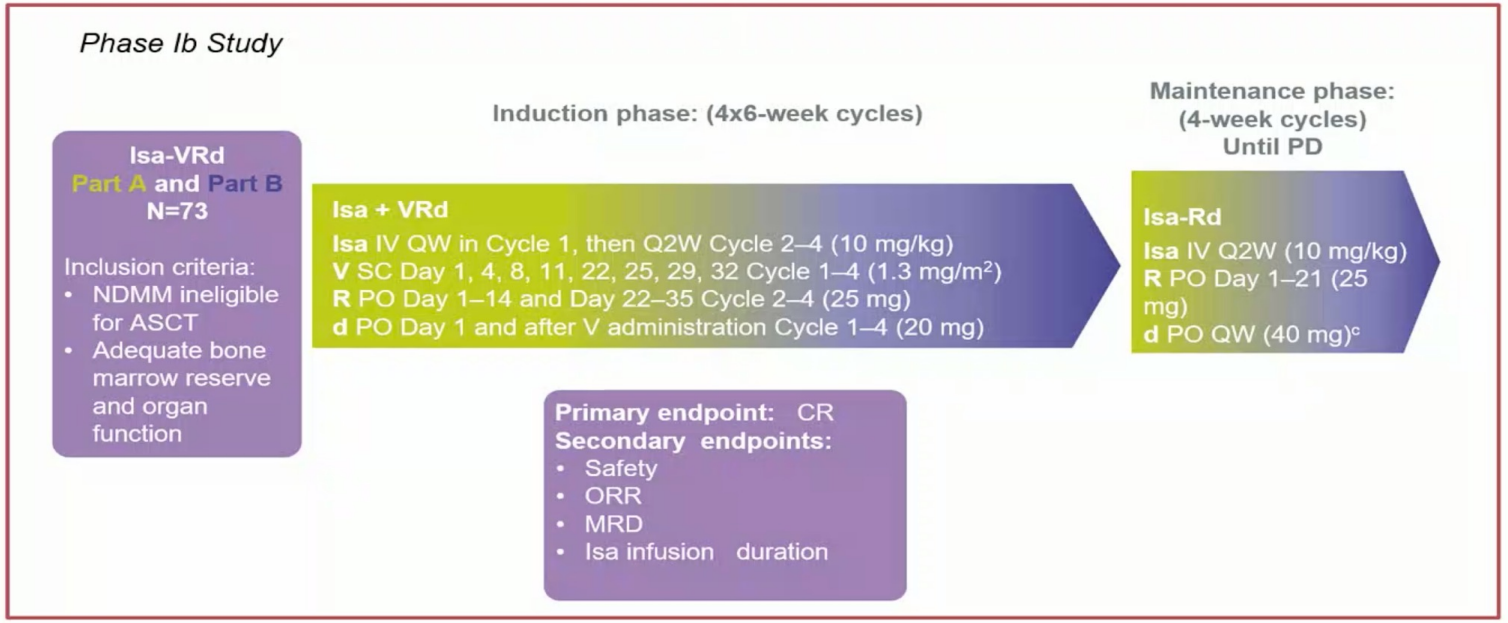
MRD-negativity



Approximately 50% and 70% of patients still failed to achieve ≥ CR and MRD negativity

Zweegman et al. - ORAL B05 - EMN 2021

New anti-CD38 containing quadruplets: Isatuximab-VRd

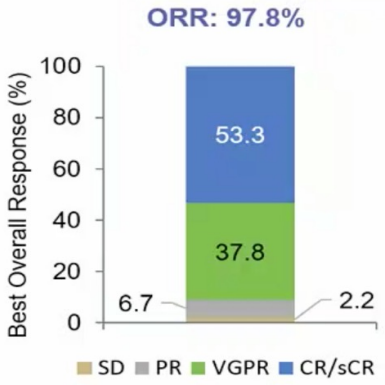


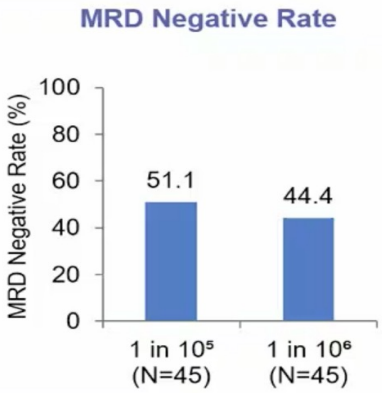
Ocio E et al, IMW 2021

New anti-CD38 containing quadruplets: Isatuximab-VRd

Patient characteristic	All-treated population (N=46)
Age in years, median (range)	70.0 (49–87)
Age in years, n (%)	
<65	8 (17.4)
≥65 to 74	30 (65.2)
≥75	8 (17.4)
Gender, female, n (%)	24 (52.2)
ECOG performance status, n (%)	
0	23 (50.0)
1	22 (47.8)
2	1 (2.2)

Median follow-up: 15.24 months





Median treatment duration, months (range)	15.3 (1.4–21.4)
Grade ≥3 TEAEs, n (%)	32 (69.6)

The ORR was 97.8%, approximately 50% of patients achieved MRD negativity

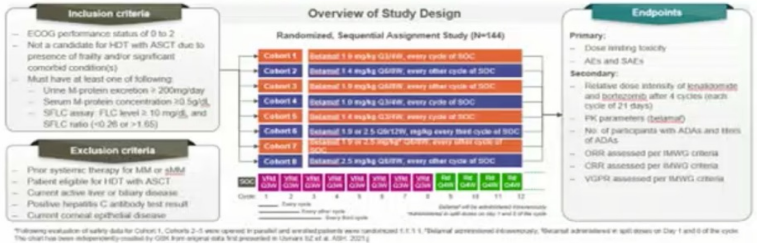
Ocio E et al, IMW 2021

Ongoing trials with anti-CD38 based quadruplets

TRIAL	REGIMEN	POPULATION	PRIMARY ENDPOINT	STATUS
IMROZ (phase III)	Isatuximab-VRD vs VRD	TNE NDMM ECOG 0-2	PFS	Enrollment completed
CEPHEUS (phase III)	Daratumumab-VRD vs VRD	TNE or TE NDMM Frailty index < 2 ECOG 0-2	MRD	Enrollment completed
IFM2020-05 (phase III)	Isa-Rd vs Isa-VRD	TNE NDMM 65-79 years ECOG 0-2	MRD	Recutiting
NCT04052880 (phase II)	Dara-VRD lite	TNE NDMM ≥ 70 years	≥ VGPR	Enrolling
GMMG CONCEPT (phase II)	TNE arm: Isatuximab-KRD and Isa-KR maintenance	TNE and TE NDMM High-risk	MRD	Enrollment completed (preliminary results at EHA 2021)
TCD13983 (phase I)	Isatuximab-VRD and Isatuximab-VCD	TNE NDMM ECOG 0-2	DLT and ORR	Enrollment completed (preliminary results at ASH 2017, 2018 and ASCO 2020)

New drugs and newer combinations

Belantamab Mafodotin Plus Standard of Care in Patients with TNE Newly Diagnosed MM
DREAMM-9: Phase I Study

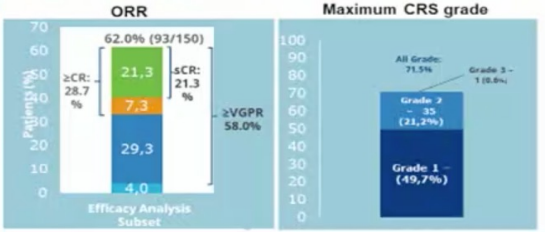


- Preliminary analysis examined 12 patients in Cohort 1 and 6 patients each in Cohorts 2-5
- Thrombocytopenia, neutropenia, and ocular symptoms were the most common events leading to dose modification
- ORR 100% in several cohorts and at least half of all patients achieving a VGPR or better in every cohort.
- Rapid responses, with some patients achieving a VGPR as early as 4 weeks into treatment

Belantamab Mafodotin Plus Rd in Patients with TNE Newly Diagnosed MM
Phase I-II Study

MajesTEC-1: a first-in-human, phase 1/2 study, to evaluate teclistamab in RRMM after ≥3 prior lines of therapy and triple-class exposed

Characteristic	Safety Analysis N=165
Age (years), median (range)	64.0 (33–84)
Age ≥75 years, n (%)	24 (14.5)
High-risk cytogenetics[a], n (%)	38 (25.9)
Time since diagnosis (years), median (range)	6.0 (0.8–22.7)
Prior lines of therapy, median (range)	5.0 (2–14)
Prior stem cell transplantation, n (%)	135 (81.8)
Exposure status, n (%)	
Triple-class exposed[f]	165 (100)
Penta-drug exposed[g]	116 (70.3)
Selinexor	6 (3.6)
Refractory status, n (%)	
Triple-class refractory[f]	128 (77.6)
Penta-drug refractory[g]	50 (30.3)
Refractory to last line of therapy	148 (89.7)



PFS rates
6 month: 64.4% (95% CI: 56.0–71.7)
9 month: 58.5% (95% CI: 48.8–67.0)

CARTITUDE-5: VRd Followed by Ciltacabtagene Autoleucel vs VRd-Rdin NDMM Not Intended for Transplant

A Randomized, Phase 3 Study: VRd + cilta-cel arm vs VRd + Rd arm (SOC)

- Eligible patients: age >18 years, ECOG <1, measurable disease; not candidates to ASCT due to advanced age or comobordities that are likely to have a negative impact on tolerability of this procedure: choose to defer ASCT as initial therapy.
- Excluded patients: frailty index >2 based on the Myeloma Geriatric Assessment Score; prior CAR-T or BCMA targeting therapy; or any prior therapy for MM or SMM

Usmani SZ, et al. ASH 2021; Moreau P et al, Abs. n 896 ASH, 2021; Dytfeld D et al., 1835 ASH 2021, Terpos et al EHA 2022

Belantamab, bispecific antibodies and CAR-T cells

Which is the optimal anti-BCMA strategy for fit, intermediate-fit and frail patients?

Belantamab

- Ongoing studies with belantamab-combinations at diagnosis
- Preliminary data suggest that belantamab may have efficacy in combination with bortezomib or lenalidomide and could be an effective combination partner with VRd

Bispecific antibodies

- Two strategies are under evaluation to improve efficacy: combination therapies and earlier use of bispecific
- Additional data are needed to evaluate the risk of infection and the long-term toxicities.

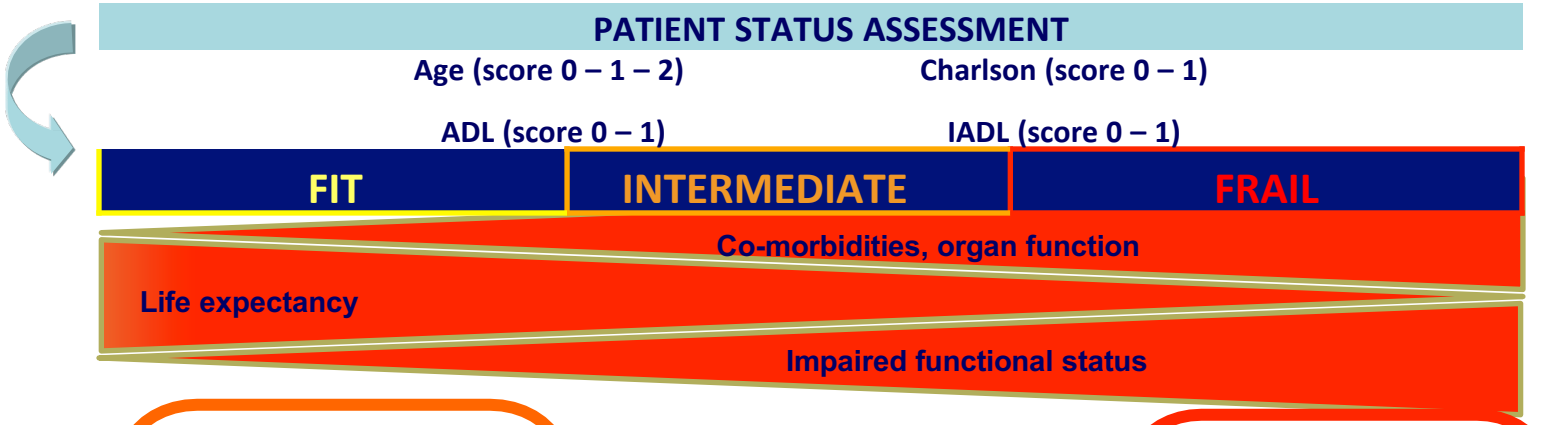
Chimeric antigen receptor (CAR)-T cell therapy

- Selected patients
- Depend on toxicity, costs and logistic (distance from an academic center and individualized manufacturing process)

Optimal treatment strategies in NTE MM patients

- **Tailored treatment based on frailty status**
  - Need uniform definition of frailty and future trials including more real-world patients
  - Modulate and adapt treatment according to frailty
  - Manage frail patients
  - Improve supportive therapies (avoid treatment discontinuation)
- **Optimal treatment sequencing**
  - Use the best treatment upfront to improve QoL in frail and outcome in fit patients
  - Increase sustained MRD-negativity to achieve longer treatment-free interval and possibly avoid second line treatment.
- **Improve the treatment strategy of NDMM**
  - Role of quadruplets (Isa-VRd better than D-VMP or D-Rd?)
  - New approaches with bispecific antibodies and CART-cell
  - More effective treatment strategies, with curative intent and a definite duration of treatment

Treatment goals based on frailty score



Goal Priority

Deep remission

Efficacy
CR/MRD-negativity

Balance efficacy/safety

Combination of efficacy/safety
Good response

Do not harm

Low toxicity
QoL

FRAILTY ASSESSMENT
IMWG Frailty Score or RMC-Index

FIT PATIENTS	INTERMEDIATE-FIT PATIENTS	FRAIL PATIENTS
		
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
Goal: efficacy	*Goal: efficacy/safety*	*Goal: safety/QoL*

APPROVED REGIMENS

Daratumumab-VMP Daratumumab-Rd VRd ASCT in pts ≤70 years old	Daratumumab-VMP, weekly V Daratumumab-Rd VRd-lite Vd	Dose-adjusted Rd ± daratumumab Dose-adjusted Vd or VMP Palliative treatment

EXPERIMENTAL REGIMENS with monoclonal antibodies

Daratumumab-VRd (NCT03652064) Isatuximab-VRd (NCT03319667) Isatuximab-VCd (NCT02513186) Belantamab-VRd (NCT04091126)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-VRd lite (NCT04052880)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-R (NCT03993912)

Bonello F et al Pharmaceuticals 2020

GRAZIE PER L'ATTENZIONE