Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

Terapia di prima linea senza trapianto autologo

Del paziente intermediate fit/frail

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Disclosures for Alessandra Larocca, MD

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Employee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	Celgene, Janssen-Cilag, Bristol-Myers Squibb, Amgen
Scientific Advisory Board	Bristol-Myer Squibb, Janssen-Cilag, Celgene, Takeda

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

Transplant ineligible myeloma patients
Background

- Recent explosion in new treatments for MM
- Data from frailty-tailored treatments are still limited
- Older patients underrepresented in clinical trials
- Little specific evidence to guide treatment decision for intermediate/frail

"Evidence-biased

as opposed to

evidence-based medicine"

The outcome of patients >75 is inferior to patients ≤75 years

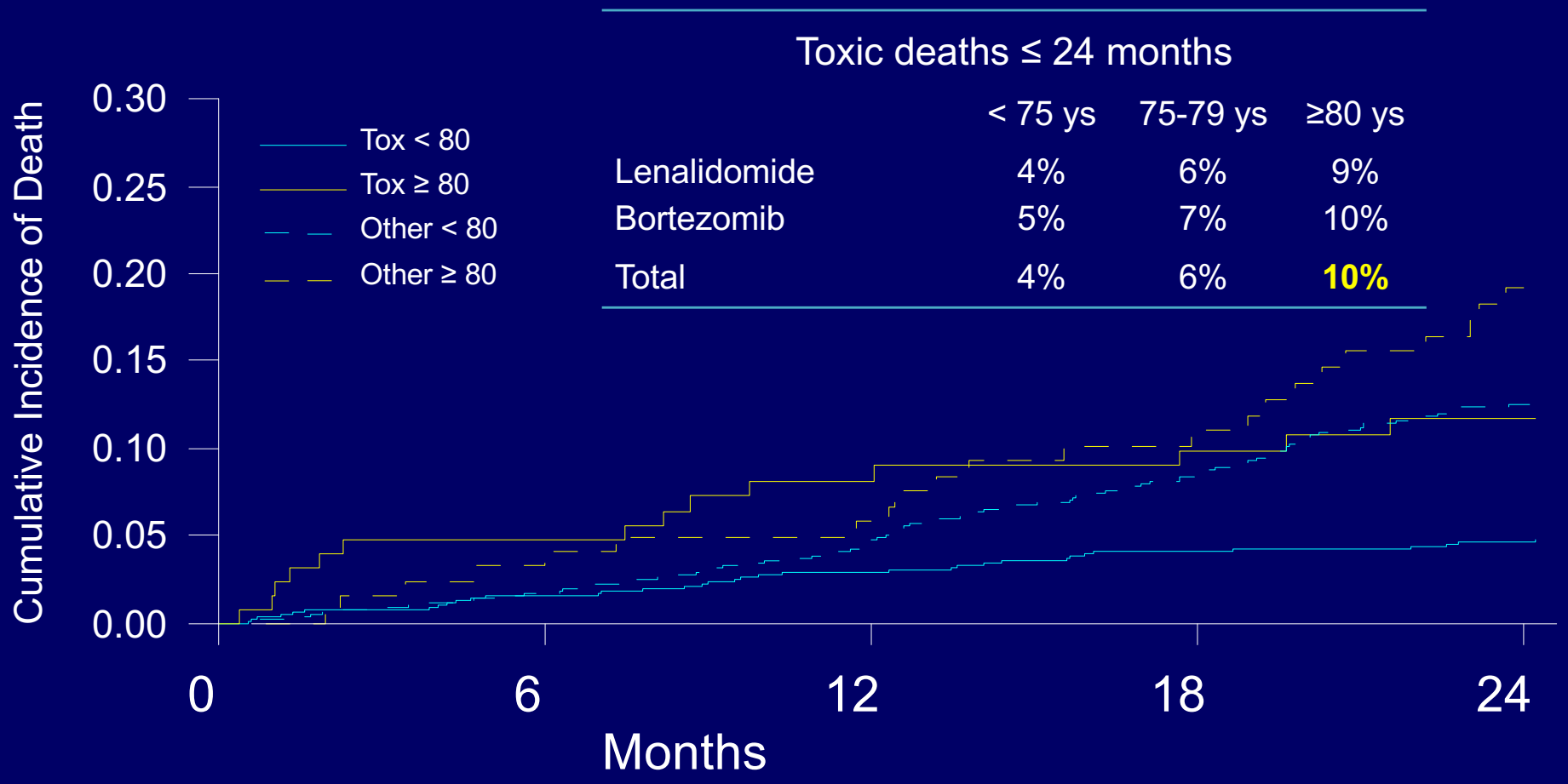
Rd continuous	Age ≤75 Years	Age >75 Years
Progression-free survival (PFS)	28 months	20 months
Overall Survival (OS)	60.9 months	52.3 months
Response Rate	82%	78%
Treatment duration (mean)	24 months	20 months
R dose reduction	37%	44%
R discontinuation	21%	26%
R full planned dose at 72 weeks	40%	30%

R, lenalidomide; d, dexamethasone.

Hulin C, et al JCO 2016. Benboubker L et al N Engl J Med 2014.

Elderly myeloma patients: age does matter

Survival inferior due to toxic deaths, thus precluding second line therapy



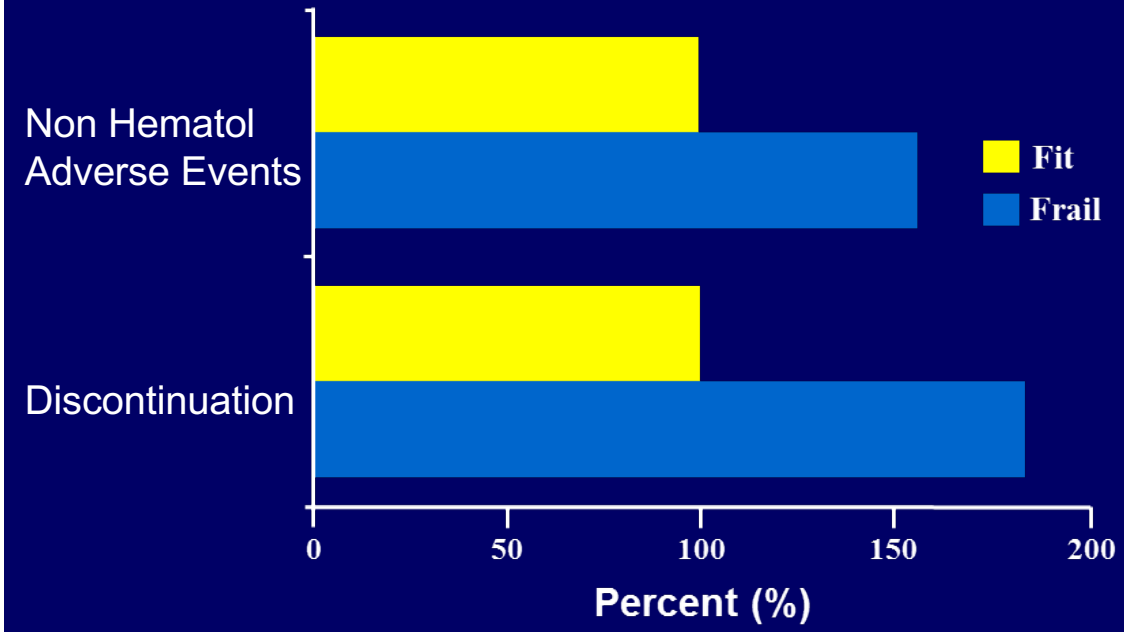
Death due to toxicity 4-fold higher and death due to other causes 2-fold higher in ≥80 versus <80 years

Bringhen S et al. Crit Rev Oncol Hematol 2018:130;27-35

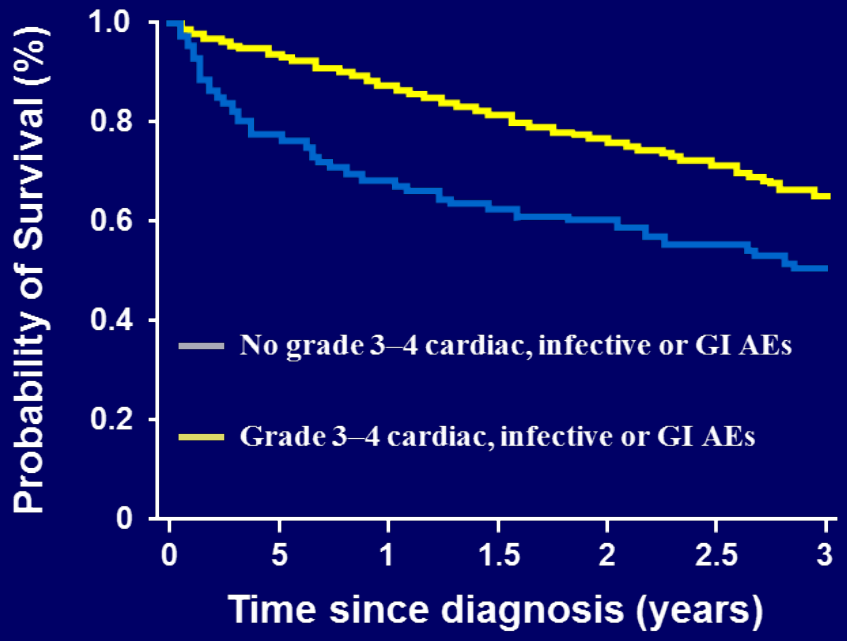
Not only chronological age affects survival

Grade 3/4 cardiac, infective, GI AEs impact on survival of 1435 myeloma patients

Grade 3-5 Adverse Events and Discontinuation



Overall Survival



CHANGE IN PARADIGM FROM AGE TO FRAILTY

*At least 1 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 and oral presentation at ASH 2013

Toxicity and compliance

Toxicity profile of standard therapies

	Any grade 3-4 Adverse Events	Discontinuation rate due to toxicity
Rd (FIRST) Continuous lenalidomide	85%	30%
MPT	75%	40%
VMP (VISTA) Bortezomib twice weekly	91%	34%
VMP (GEM-2005) Bortezomib once weekly	NA	17%
VMP (GIMEMA) Bortezomib once weekly	51%	17%

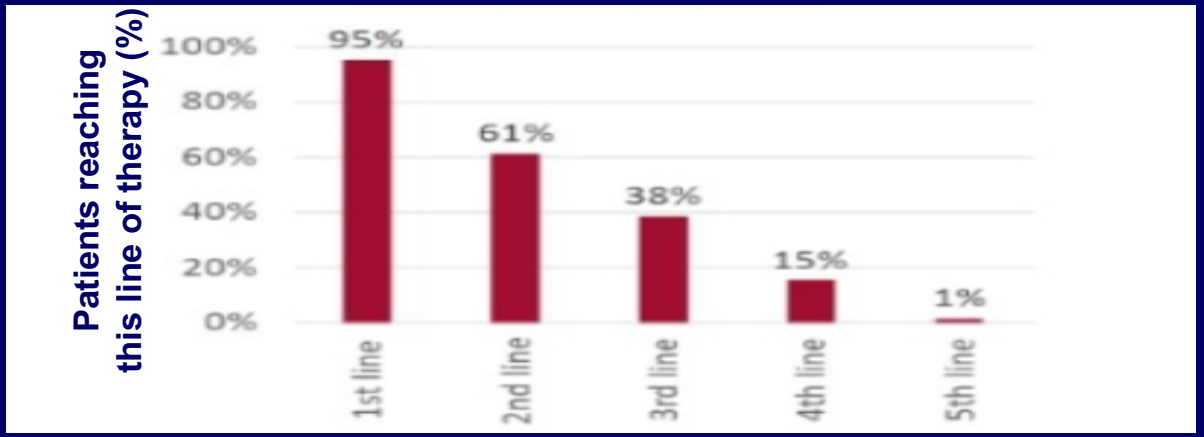
Benboubker L et al. NEJM 371;10, 2014
Fayers PM, Blood 2011;118:1239-1247.
San Miguel JF, et al. N Engl J Med 2008; 359:906–917.
Mateos MV, et al. Lancet Oncol. 2010;11:934-41.
Palumbo A., et al. J Clin Oncol 2010; 28:5101-9.

Treatment Outcome in Real World Practice

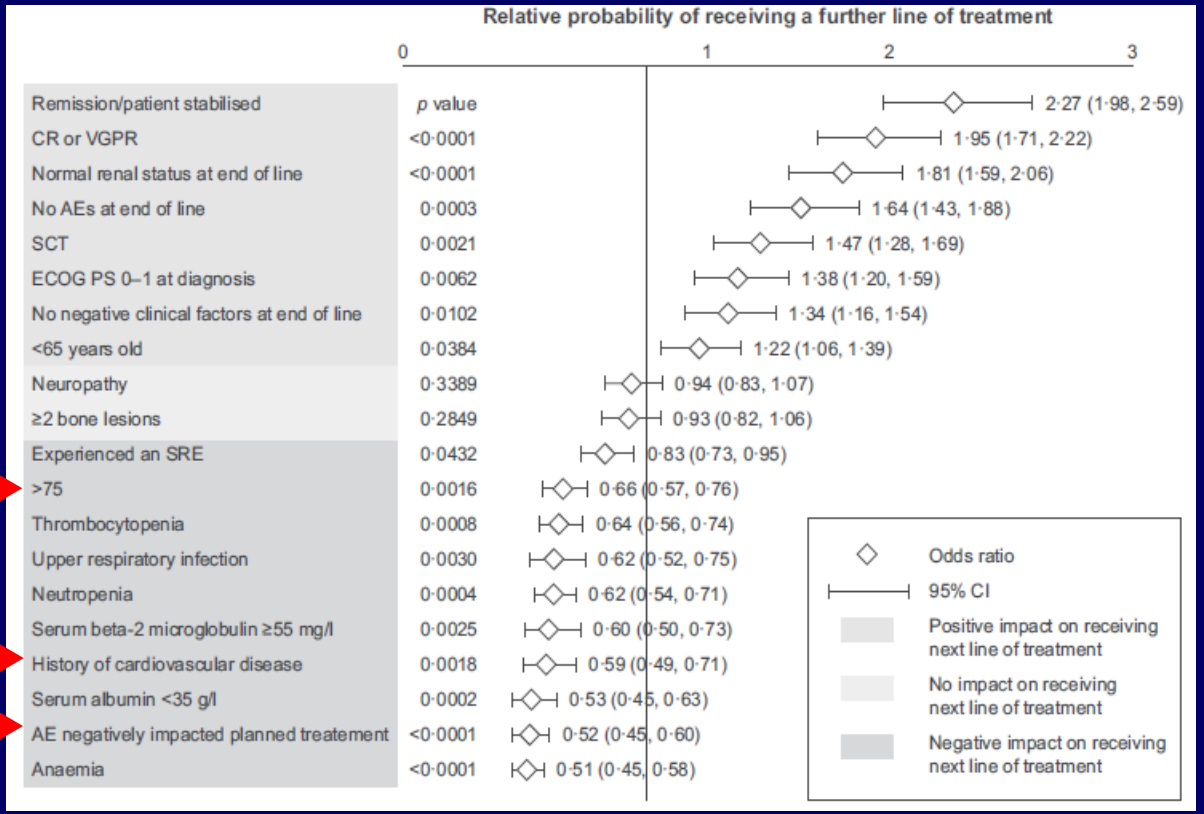
Importance of first -line treatment

4997 patients

Age<65 years 36%
65-75 years 42%
>75 years 22%



Association of patient characteristics with the probability of receiving a further line of treatment



Yong K et al British Journal of Haematology, 2016, 175, 252–264

Patient-defined goals and preferences

Older adults with cancer starting chemotherapy

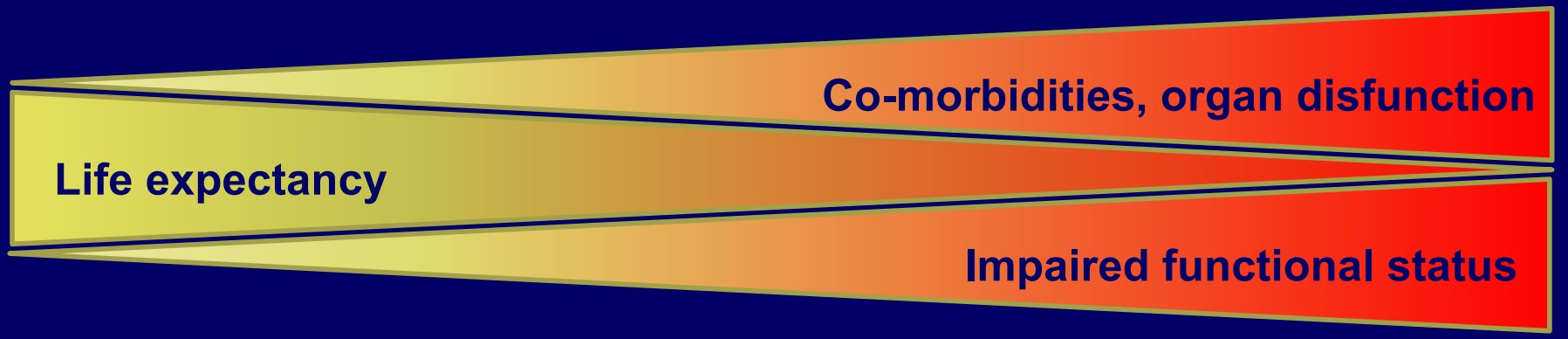
Attitude scale (n = 121)

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 Journal of Clinical Oncology2018, 36, no. 15_suppl

Treatment goals in elderly MM patients

FIT	INTERMEDIATE	FRAIL



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

Treatment strategies for intermediate and frail MM patients

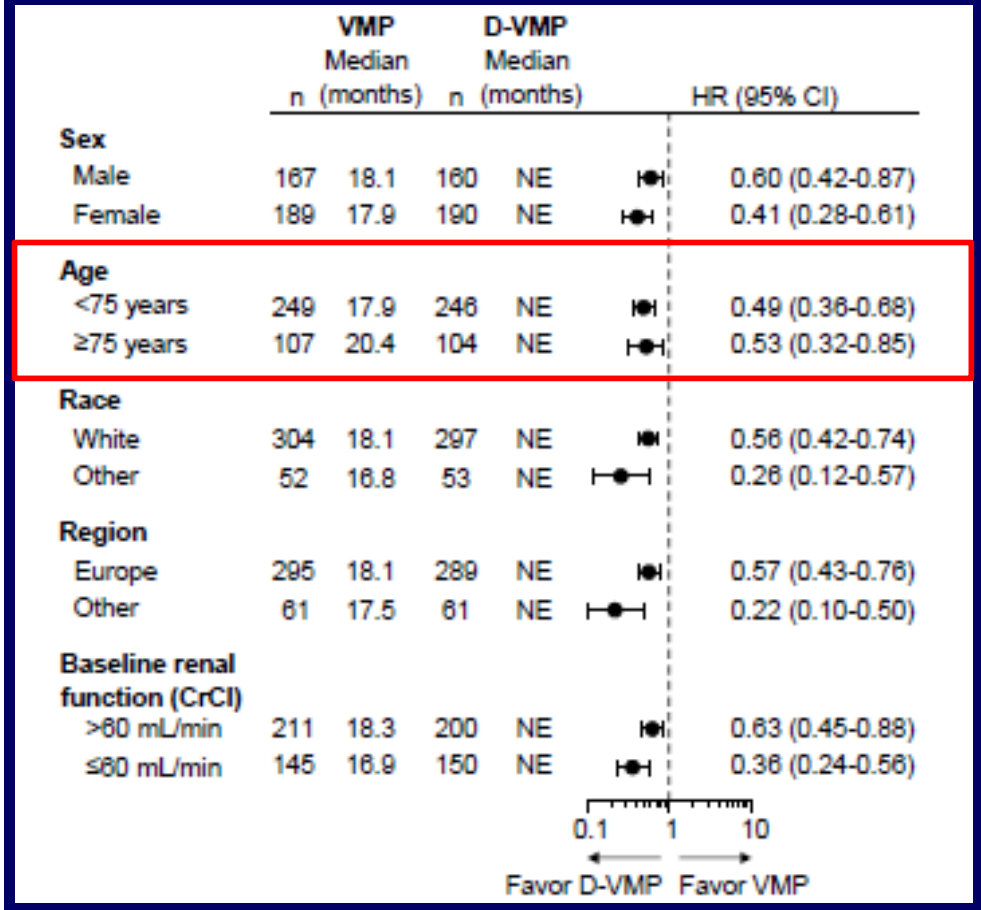
- Does one treatment fit for all patients?
- Appropriate duration of treatment?
- Optimal dose and schedule adjustments to avoid severe toxicities?
- “Non frail” drugs?

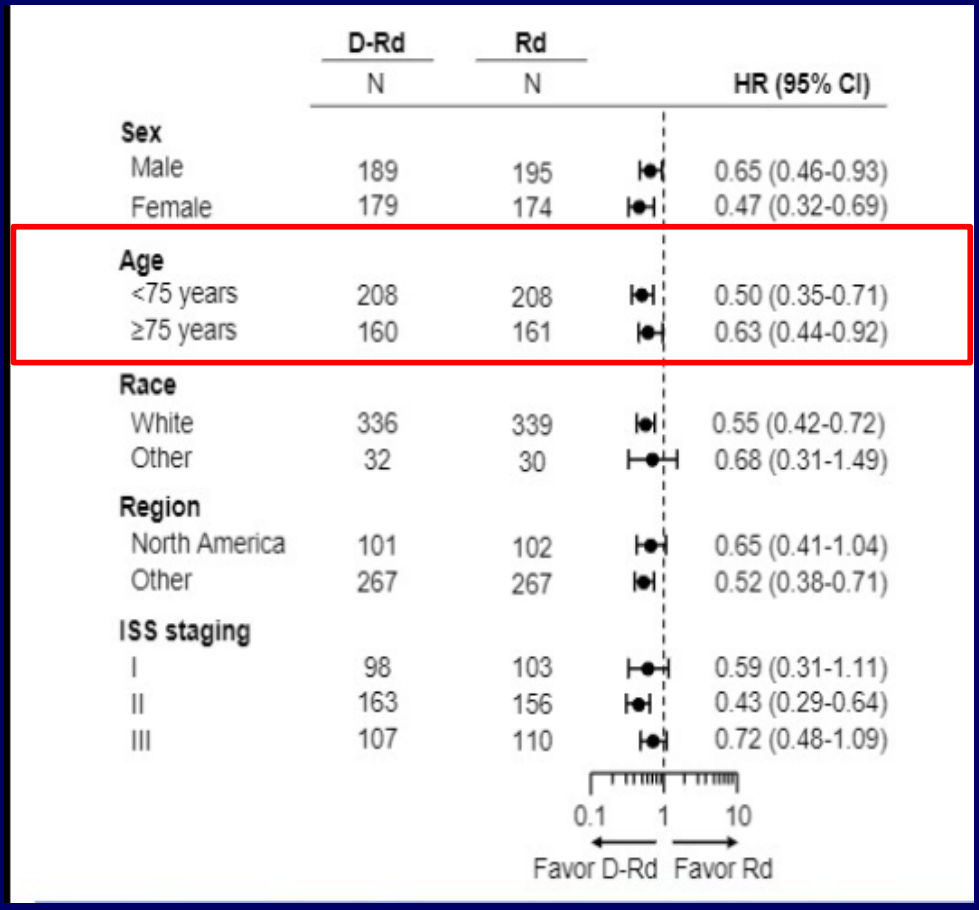
Antibody-based therapy is safe and active in elderly patients

ALCYONE Daratumumab-VMP vs VMP

MAYA Daratumumab-Rd vs Rd

Efficacy: PFS in pre-specified subgroups





No impact of age was observed

Mateos MV et al .NEJM 2017

Facon T et al. ASH 2018

Antibody-based therapy is safe and active in elderly patients

ALCYONE Daratumumab-VMP vs VMP

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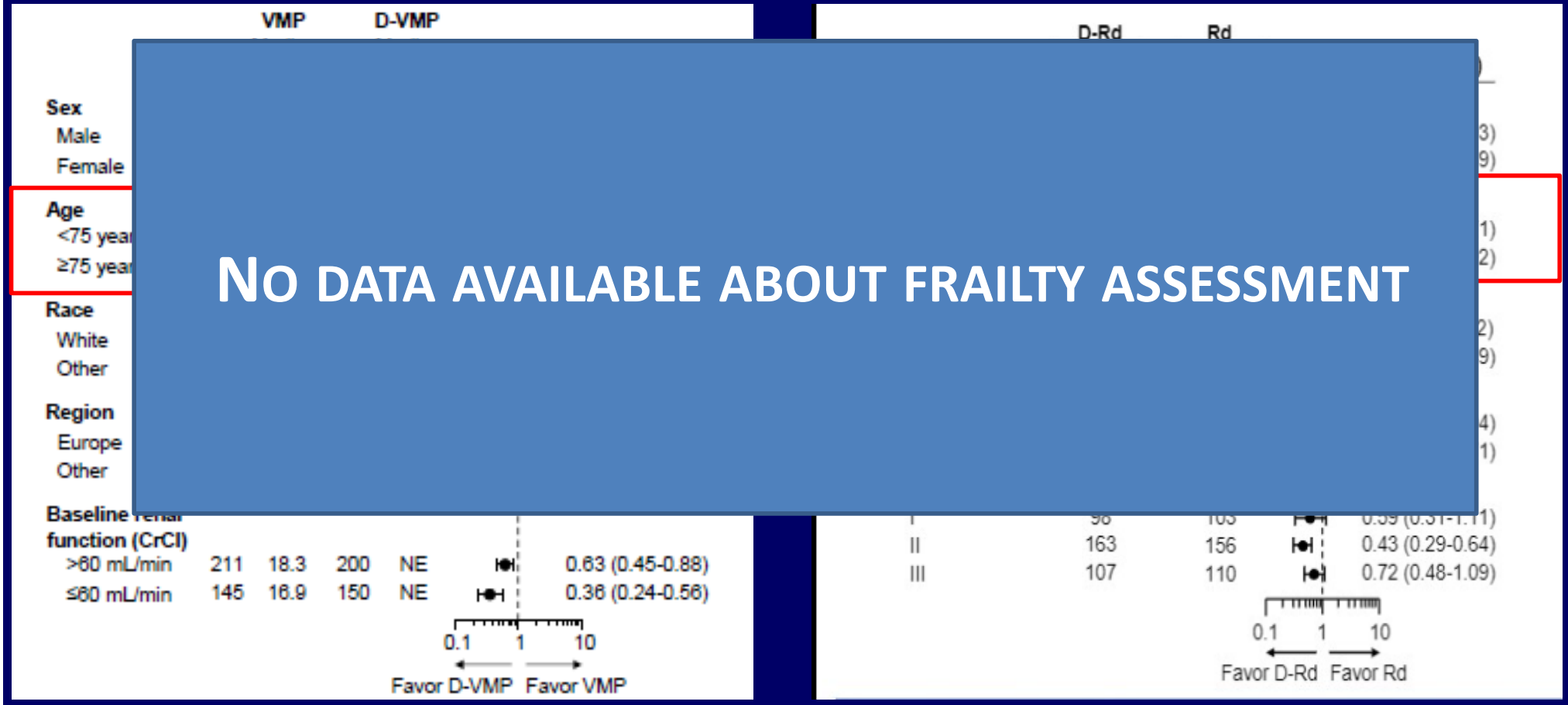
Efficacy: PFS in pre-specified subgroups



NO DATA AVAILABLE ABOUT FRAILTY ASSESSMENT

No impact of age was observed

Mateos MV et al .NEJM 2017

Facon T et al. ASH 2018

Ixazomib-Daratumumab-low dose Dexamethasone in Unfit and Frail NDMM patients

Phase II HOVON 143 trial

Study Design

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 tid
Vaccinations

- Median age 76 years for unfit and 82 years for frail patients
- Efficacy data for first 10 unfit and10 frail patients who completed first 4 cycles
- Preliminary SAE and mortality analysis of all 104 patients, median follow-up: 3.8 months for unfit and 1.8 months for frail patients

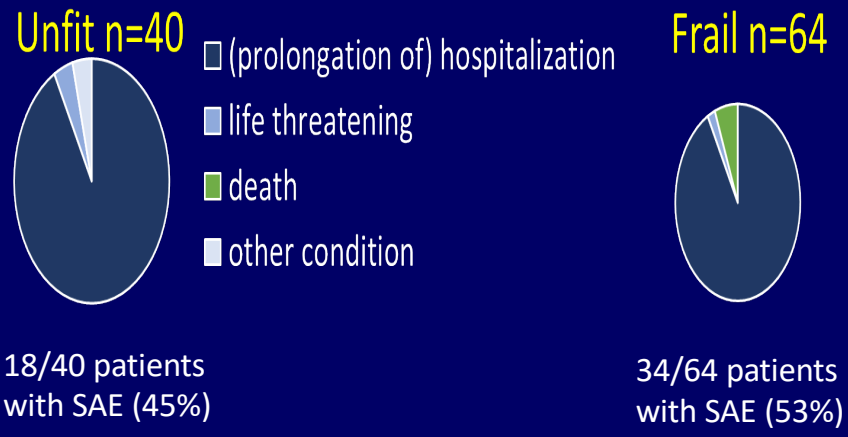
Stege CAM , Zweegman S et al, ASH 2018

Ixazomib-Daratumumab-low dose Dexamethasone in Unfit and Frail NDMM patients

Response after 4 induction cycles

Response rate (%)	Unfit (n=10)	Frail (n=10)
≥VGPR	30	20
>PR	100	80
SD	-	10
PD	-	-
Not evaluable	-	10
Median time to response (months)	2	1

SAE rate in unfit and frail mainly due to hospitalization



- Feasible treatment in both unfit and frail NDMM patients
- Grade 3/4 hematologic toxicity limited; none in unfit, thrombocytopenia 40% and neutropenia 20% in frail patients
- Grade 3-5 non-hematologic AEs in 7/10 frail patients; Infections and cardiotoxicity most frequent
- Low preliminary mortality rate of 6.7%, mostly in frail (9.4%) vs unfit patients (2.5%)
- Preliminary analysis shows promising ORR after first 4 induction cycles

Stege CAM et al., ASH 2018, abs 596

Ixazomib-Daratumumab-low dose Dexamethasone in Unfit and Frail NDMM patients

Grade III and IV Non-hematological toxicity

of the first 10 unfit and 10 frail patients completing 4 induction cycles

	Unfit (n=10)		Frail (n=10)	
CTCAE	**III (5)**	**IV (1)**	**III (6)**	**IV-V (1)**
Infections	upper respiratory infection (1)	influenza (1)	-	-
Cardiac	atrial fibrillation (1) myocardial ischemia (1)	-	-	-
Gastro-intestinal	-	-	diarrhea (1)	-
Renal	-	-	acute renal failure (1)	-
Other	hyperglycaemia (1) pain (1)	-	depression (1) confusion (1) PE (1) GI bleeding (1)	sudden death (1)

Stege CAM , Zweegman S et al, ASH 2018

Ixazomib-Daratumumab-low dose Dexamethasone in Unfit and Frail NDMM patients

GRADE III AND IV NON-HEMATOLOGICAL TOXICITY

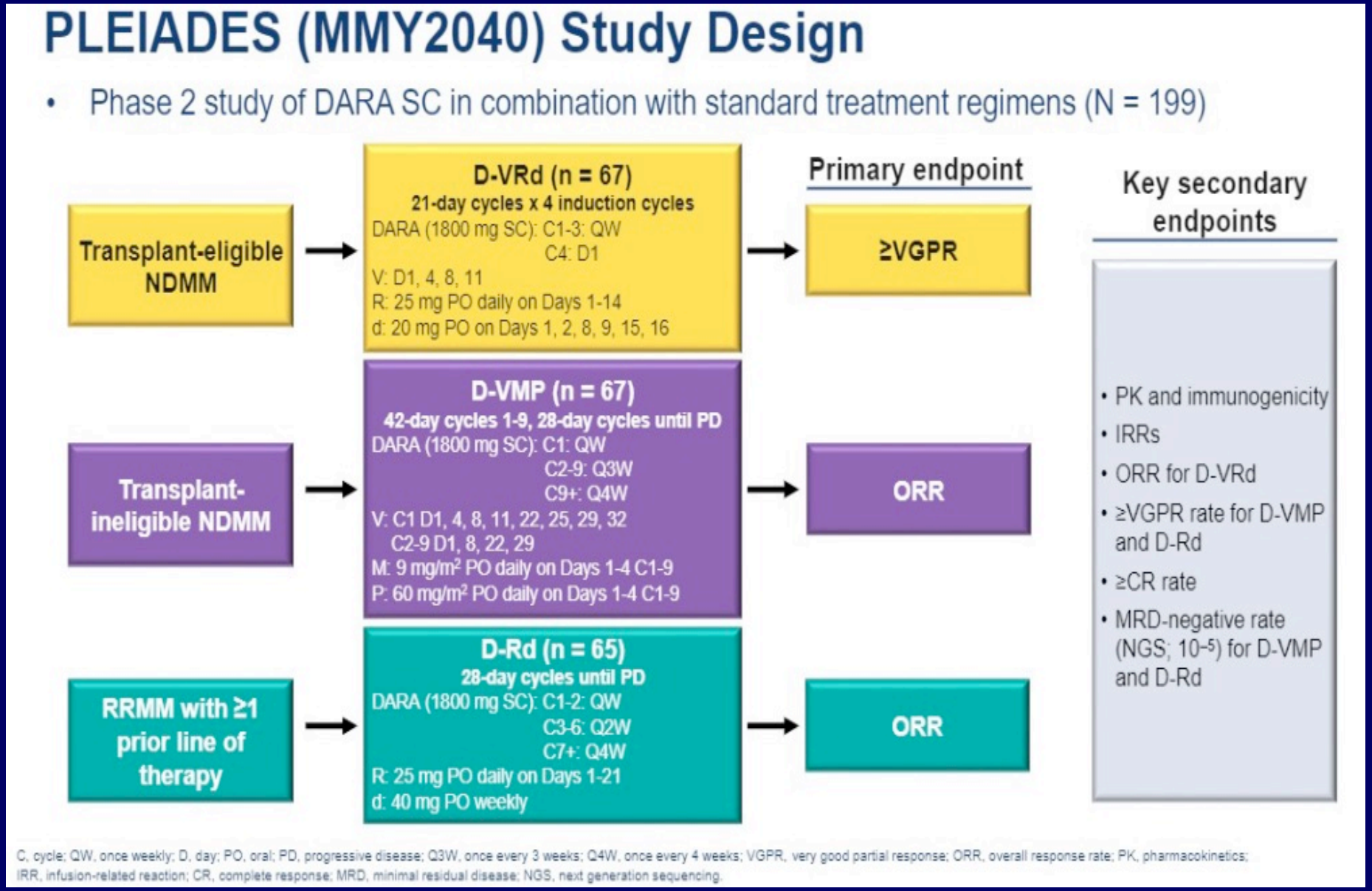
OF THE FIRST 10 UNFIT AND 10 FRAIL PATIENTS COMPLETING 4 INDUCTION CYCLES

	Unfit (n=10)	Frail (n=10)
CT		
Infe		
Car		
Gas inte		
Ren		
Othe	pain (1)	depression (1) confusion (1) PE (1) GI bleeding (1)

STRATEGY OF USING LESS TOXIC NON FRAIL DRUGS

Stege CAM , Zweegman S et al, ASH 2018

Daratumumab: optimizing administration



C, cycle; QW, once weekly; D, day; PO, oral; PD, progressive disease; Q3W, once every 3 weeks; Q4W, once every 4 weeks; VGPR, very good partial response; ORR, overall response rate; PK, pharmacokinetics; IRR, infusion-related reaction; CR, complete response; MRD, minimal residual disease; NGS, next generation sequencing.

Daratumumab: optimizing administration

Safety Summary

	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)

- IRRs occurred in 7.5% (15/199) of patients across all cohorts
  - 93.3% (14/15) of patients with IRRs experienced them on the first administration
  - IRRs were mild (grade 1/2) in 93.3% (14/15) of patients; 1 patient had a grade 3 IRR leading to discontinuation of DARA SC, and no patient had a grade 4 IRR
- Median time to onset of IRRs was 3.3 hours
  - Patients were not required to stay for observation beyond the first administration of DARA SC
- Local injection-site reactions occurred in 7.5% (15/199) of patients across all cohorts (all grade 1/2)

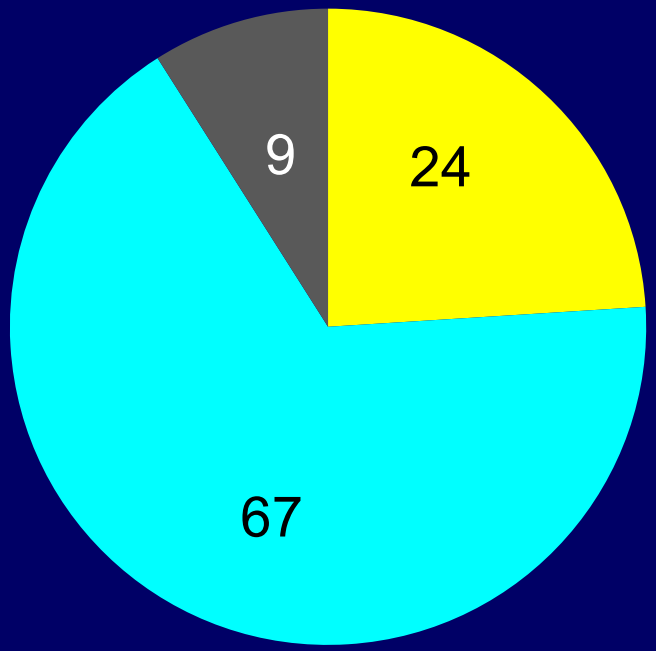
DARA SC combination therapy safety profiles were consistent with DARA IV, with lower rates of IRRs

TEAE, treatment-emergent adverse event.
All safety data are based on the 4-month safety update.

Duration of treatment

Outcome of 9 cycles of Dose-Adjusted VMP In unfit and frail patients

HOVON 123 study in patients ≥ 75 years



6 cycles of VMP were feasible in 70% of all patients

with comparable ORR and ≥ VGPR

1. No fit patients were included, because all patients were > 75 years
2. Of the 64 frail patients, 44% was aged 75-80 and 13% was frail because of being >80 years only

Zweegman S, et al. ASH 2016 (Abstract 3305)

Duration of treatment

Outcome of 9 cycles of Dose-Adjusted VMP In unfit and frail patients

HOVON 123 study in patients ≥ 75 years

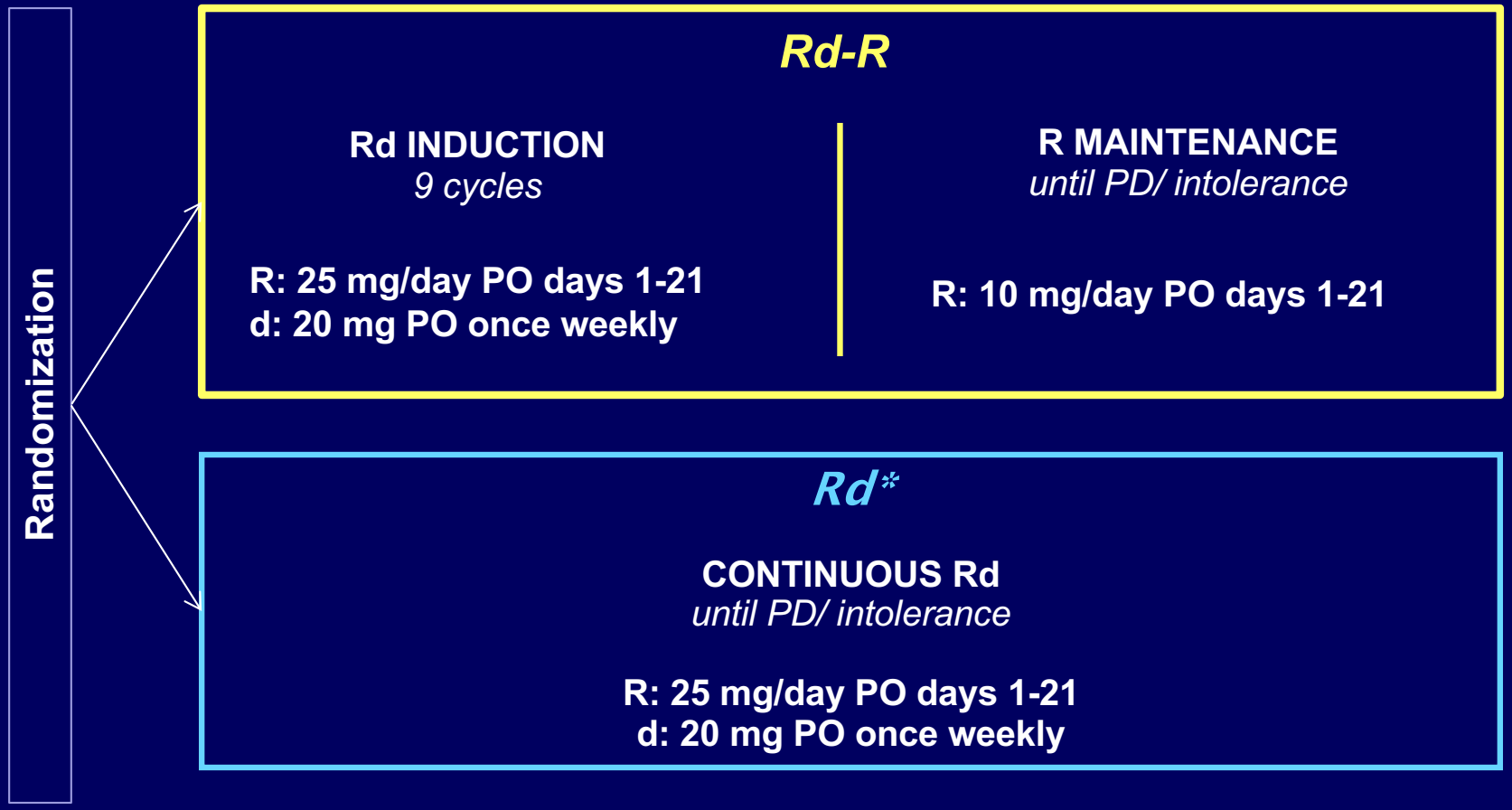
A LIMITED INDUCTION TREATMENT MAY BE FEASIBLE IN MOST OF UNFIT/FRAIL PATIENTS

1. No fit patients were included, because all patients were > 75 years
2. Of the 64 frail patients, 44% was aged 75-80 and 13% was frail because of being >80 years only

Zweegman S, et al. ASH 2016 (Abstract 3305)

Dose/Schedule-Adjusted Rd-R Vs. Continuous Rd in Elderly and Intermediate-Fit (Unfit) Newly Diagnosed Multiple Myeloma Patients: RV-MM-PI-0752 Phase III Randomized Study

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

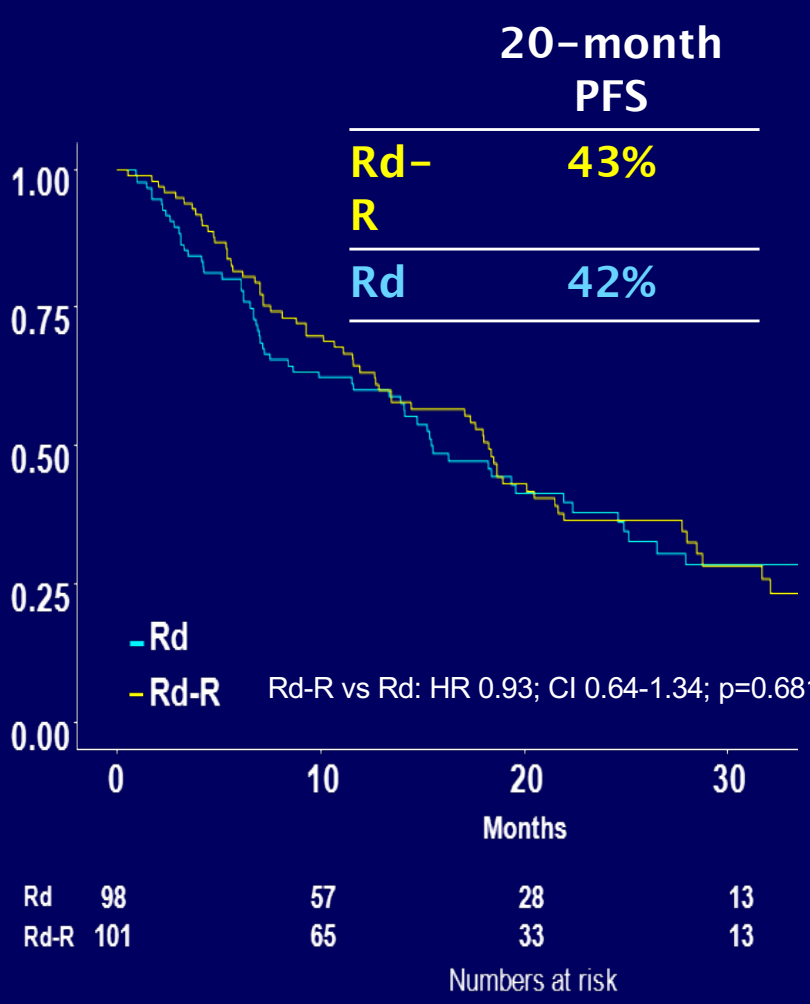


*The dose and schedule of continuous Rd was the one adopted in patients >75 years in the FIRST trial (Hulin C et al. JCO 2016)

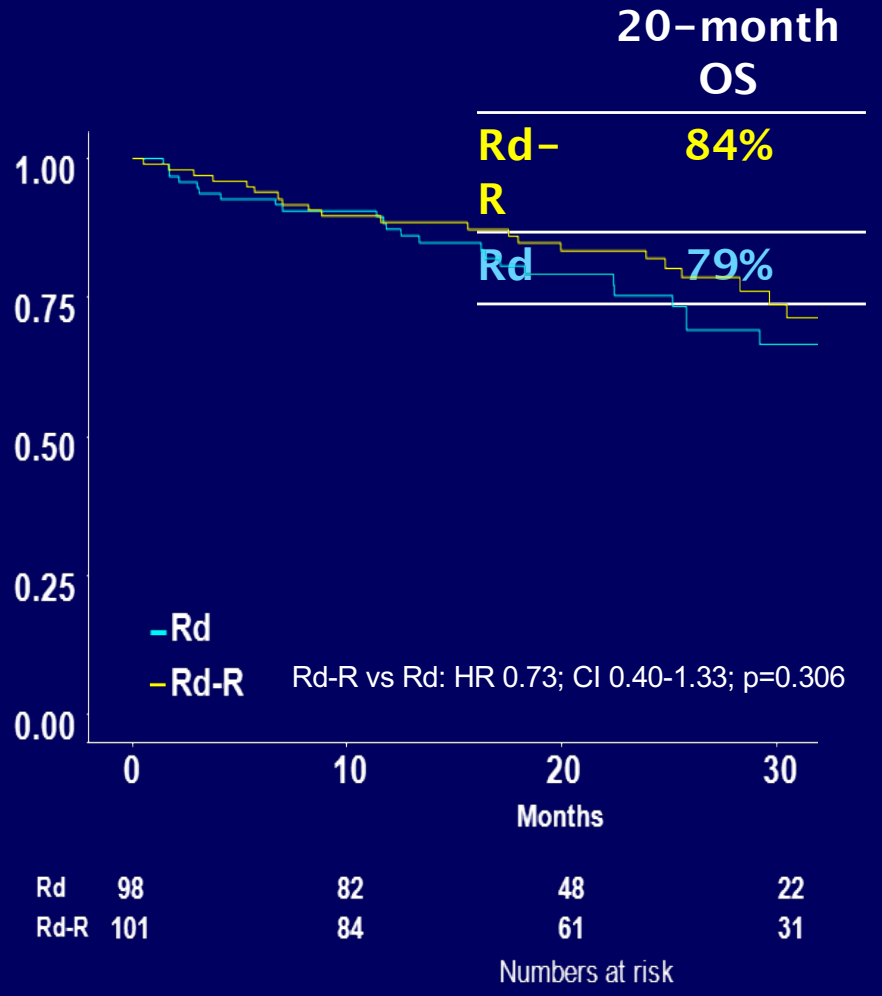
R, lenalidomide; d, dexamethasone; PO, orally; PD, progressive disease

Rd-R vs Rd

Progression-free survival



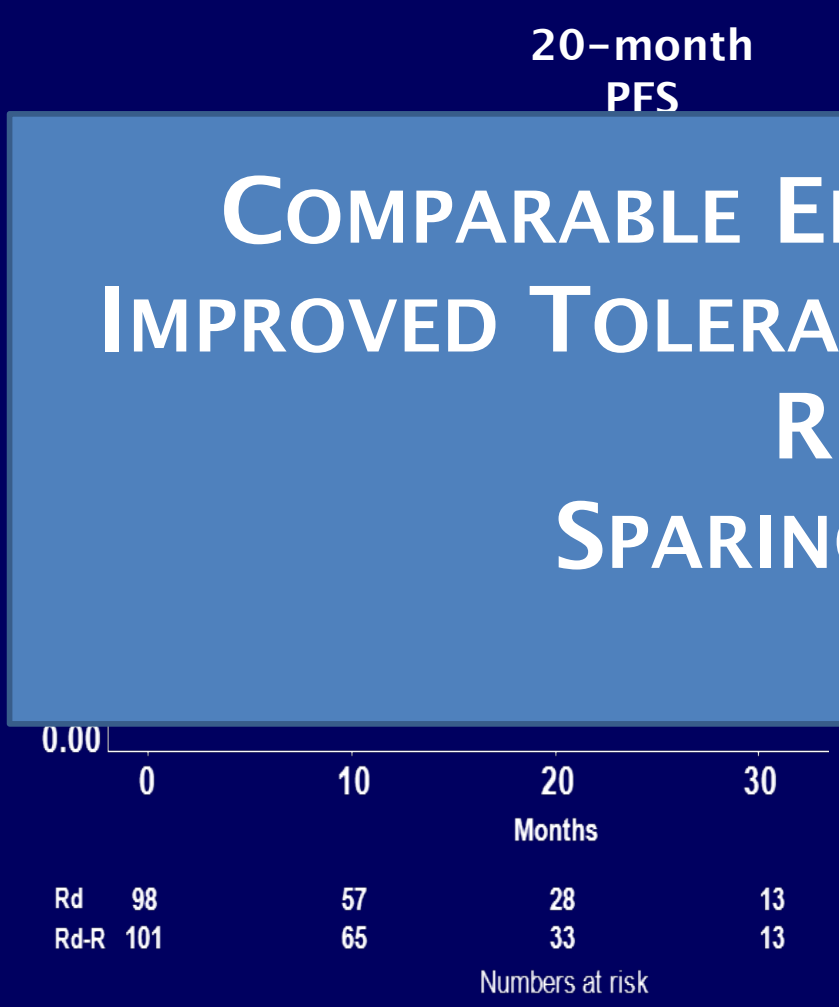
Overall survival



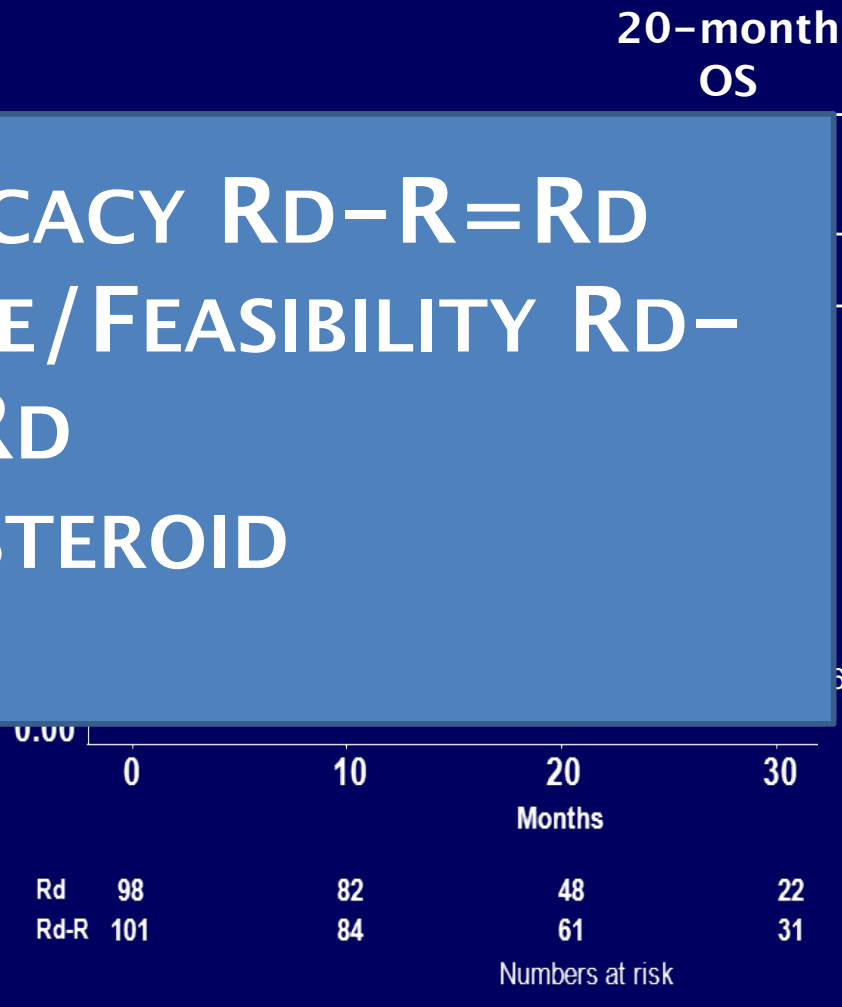
R, Lenalidomide; d, dexamethasone; PFS, progression-free survival, OS, overall survival.

Rd-R vs Rd

Progression-free survival



Overall survival



COMPARABLE EFFICACY RD-R=RD
IMPROVED TOLERANCE/FEASIBILITY RD-R>RD
SPARING STEROID

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

Proposed dose reductions

Expert consideration of treatment adjustment based on patient frailty

	FIT	UNFIT	FRAIL
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 Day 1, 4, 8, 11 every 3 weeks	1.3 mg/m^2 once weekly Day 1, 8, 15, 22 every 5 weeks	1.0 mg/m^2 once weekly 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 1+15, 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 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 1+2, from cycle 3: day 1+15
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

Zweegman S, Engelhardt M, Larocca A. EHA SWG on 'Aging and Hematology'. Curr Opin Oncol. 2017 .

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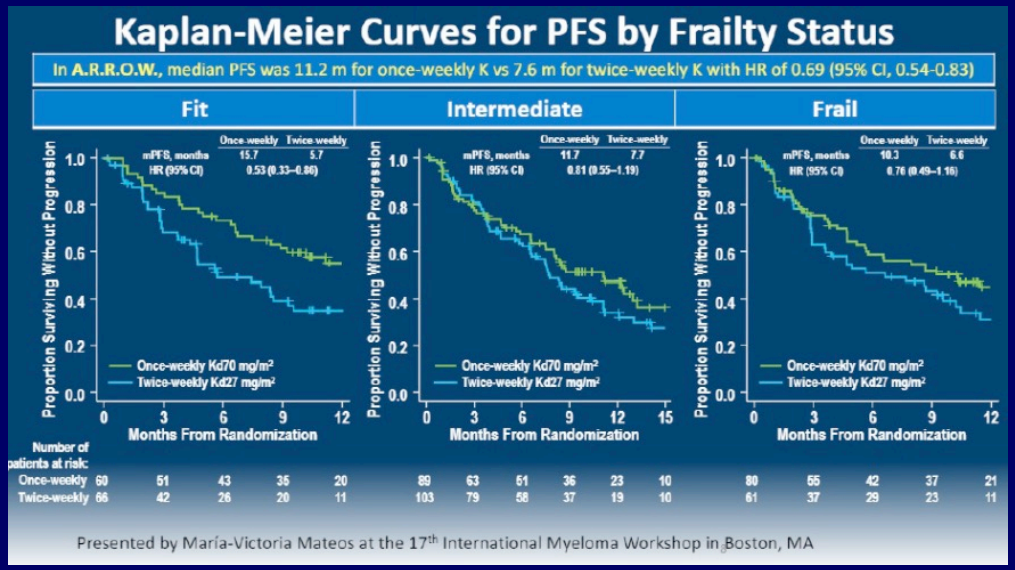
Panobinostat	20 mg day 1, 3, 5, 8, 10, 12 every 4 weeks	15 mg day 1, 3, 5, 8, 10, 12 every 4 weeks	10 mg day 1, 3, 5, 8, 10, 12 every 5 weeks

FOR FRAIL PATIENTS, STARTING AT LOWER DOSES AND INCREASING THE DOSE IF GOOD TOLERANCE?

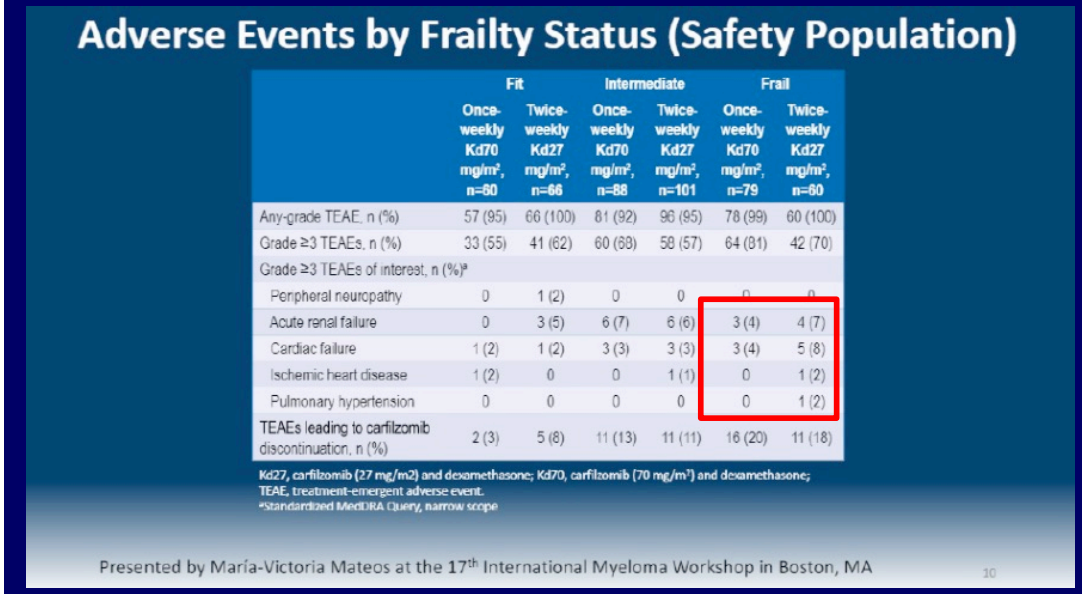
Zweegman S, Engelhardt M, Larocca A. EHA SWG on 'Aging and Hematology'. Curr Opin Oncol. 2017 .

ARROW

Strategy of ‘new treatment schedule’ once weekly Carfilzomib



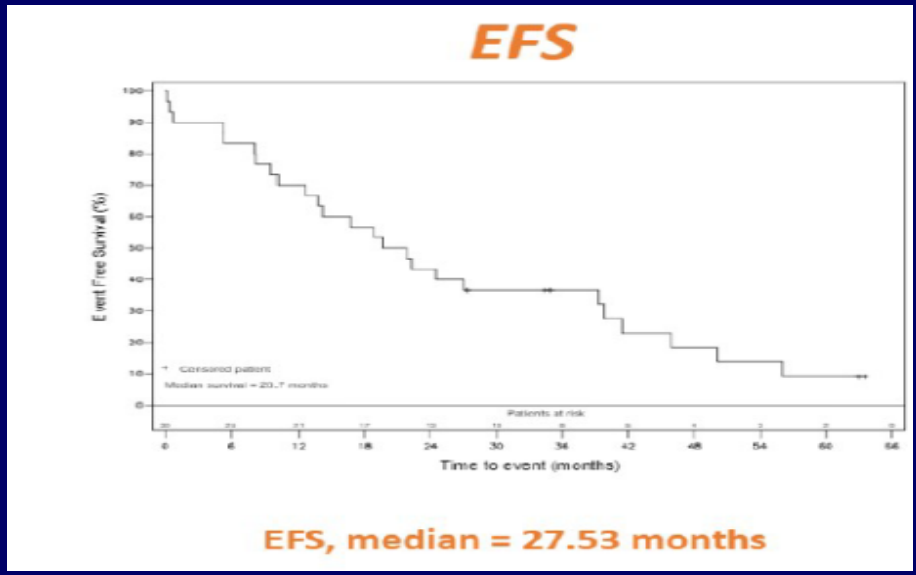
Presented by María-Victoria Mateos at the 17th International Myeloma Workshop in Boston, MA

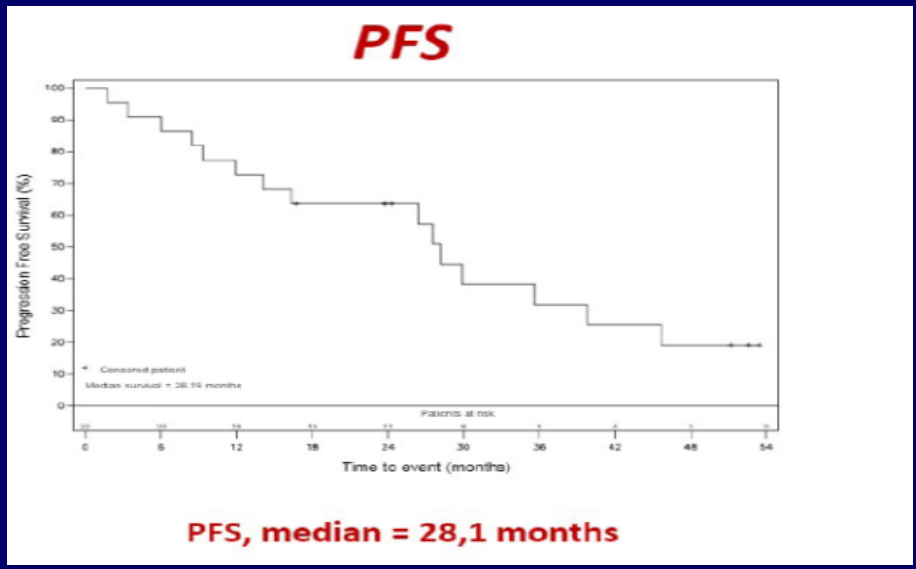


Presented by María-Victoria Mateos at the 17th International Myeloma Workshop in Boston, MA

IFM-2012-03

Strategy of ‘prolonged tolerable therapy’ with Carfilzomib maintenance





Mteos MV IMWG 2019: Leleu X IMWG 2019

Treatment algorithm based on Frailty Assessment

PATIENT STATUS ASSESSMENT

Age (score 0 – 1 – 2) Charlson (score 0 – 1)

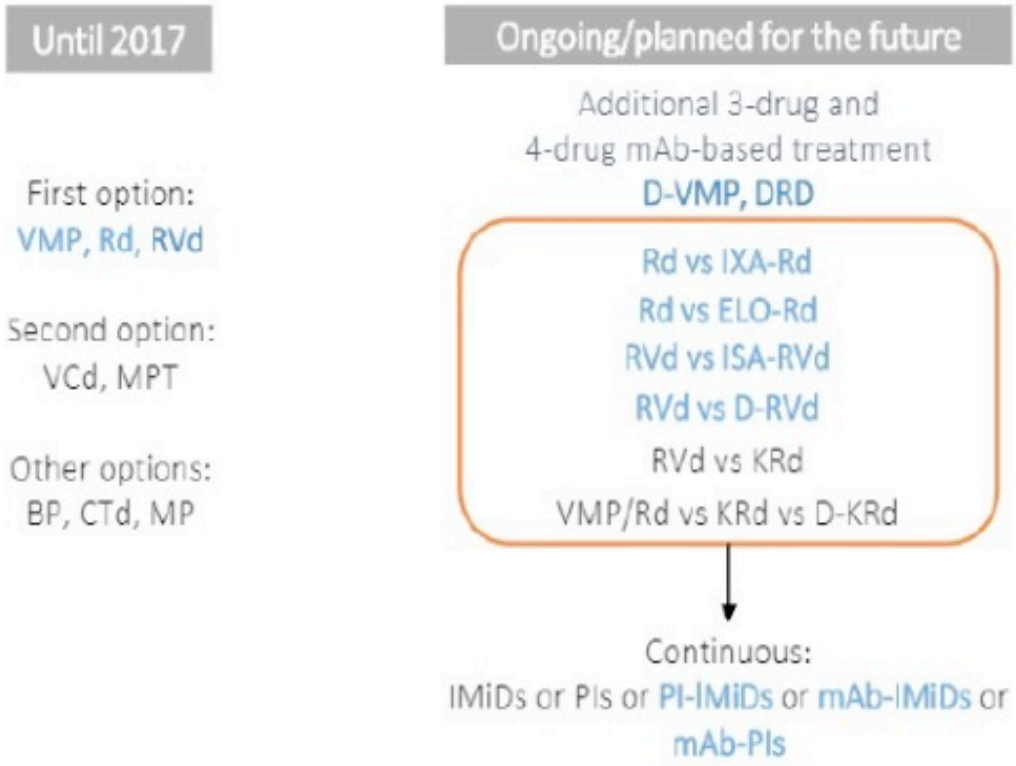
ADL (score 0 – 1) IADL (score 0 – 1)

FIT	INTERMEDIATE	FRAIL
Additive total score = 0	Additive total score = 1	Additive total score ≥ 2
Full-dose	Full-dose/Reduced	Reduced dose
TRIPLET REGIMENS ASCT VMP Rd VRD	**DOUBLET REGIMENS** Rd //Rd-R Vd Reduced-dose triplet	**Doublet regimens** rd Vd Palliative/supportive

EMN consensus; Larocca A et al. Leukemia 2018

…also for Frail patients

Current and potential future treatment algorithms for transplant-ineligible MM patients



Moreau P, et al. Ann Oncol 2017;28 Suppl 4:iv52-iv61.
Cavo M, personal communication.
ClinicalTrials.gov Identifiers: NCT02874742; NCT02541383; NCT02495922; NCT01863550.

ixazomib.

Future trials

Frailty-tailored treatments

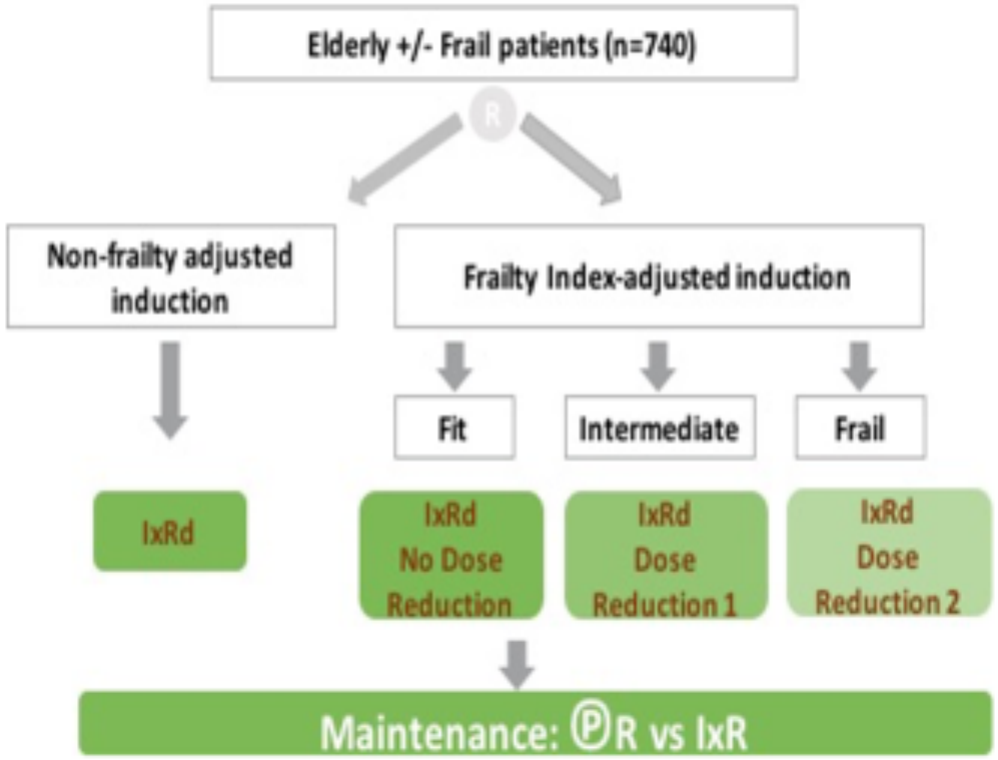
Frailty-adjusted dosing

Myeloma XIV – ***FITNEsS***

Frailty-adjusted therapy **I**n **T**ransplant **N**on-**E**ligible patient**S** with **S**ymptomatic myeloma

FiTNEss
UK-MRA Myeloma XIV

CANCER RESEARCH UK



NCRI National Cancer Research Institute

PI: Prof Gordon Cook & Prof Graham Jackson

UK MYELOMA RESEARCH ALLIANCE

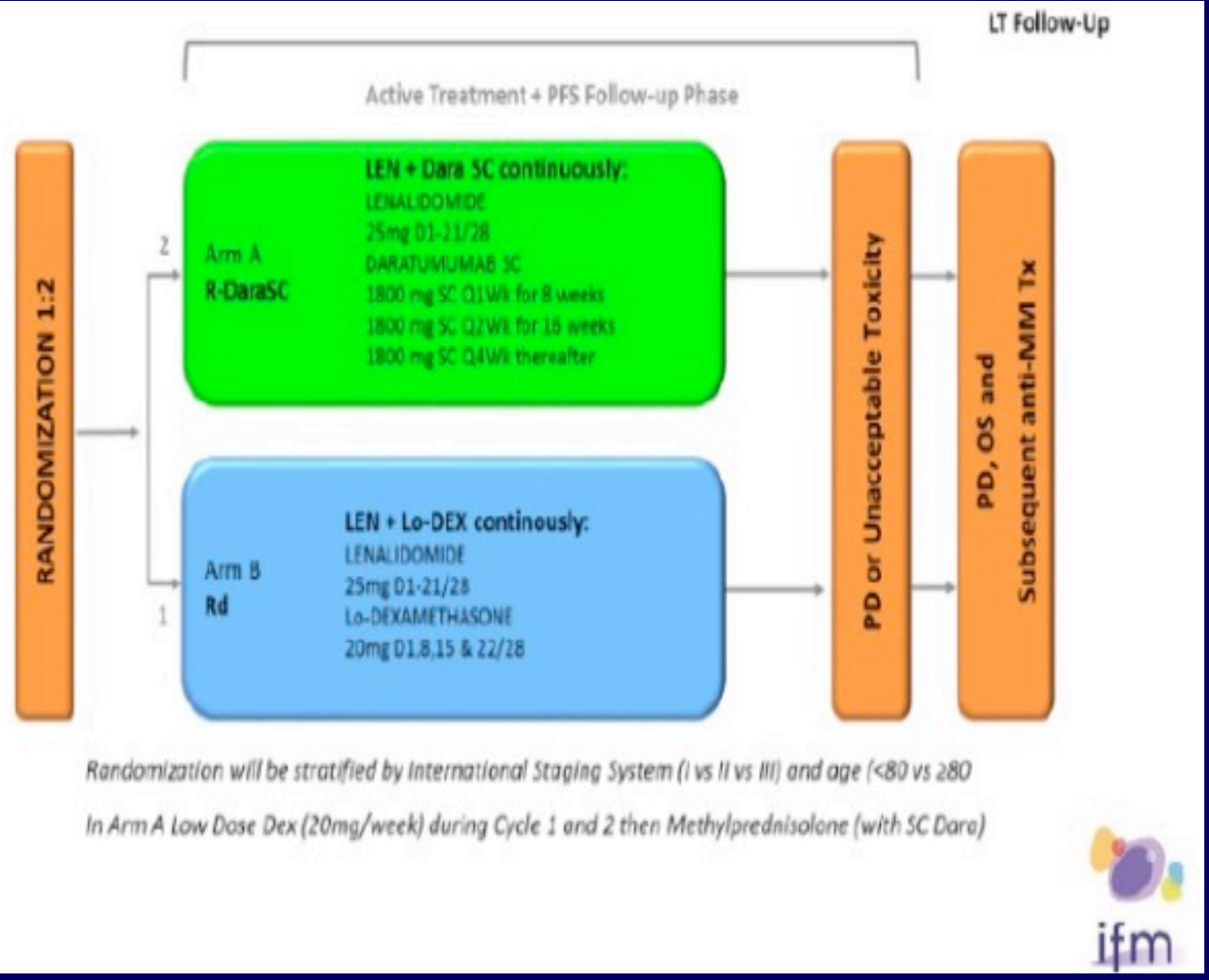
Frail patients

Using "non frail" drugs and dexamethasone sparing strategy

IFM 2017-03

340 patients

Primary endpoint - PFS



Treatment Decision Process
Unfit/Frail patients

Patients
- **ADL**
- **IADL**
- **Comorbidities**
- **Hospitalization**
- **Medications**
- **Social Support**
- **Sarcopenia**
- **Biologic markers**

Multiple Myeloma
- Cytogenetics
- Stage
- Tumor burden

Goals of Care
- **CR vs Disease Control**
- Expectations

Second Generation New Drugs

Comorbidities: cardiovascular Karf!
pulmonary functions MoAb!

Compliance +Ixazomib

Toxicities

Neuropathy + Karf
DVT/PE +MoAb
Cardiac toxicity +MoAb

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3.	**ASCOLI PICENO**	Galieni
4.	**ASTI**	Saracco, Marchetti
5.	**AVELLINO**	Cantore, Volpe
6.	**AVIANO**	Micheli, Rupolo
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8.	**BARI**	Specchia
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42.	**MILANO**	Cairoli, Cafro
43.	**MILANO**	Ciceri
44.	**MILANO**	Cortelezzi, Baldini
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47.	**MONZA**	Passerini, Rossini
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49.	**NAPOLI**	Ferrara, Rocco
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66.	**RIMINI**	Tosi
67.	**RIONERO**	Musto
68.	**RIETI**	Ceribelli
69.	**ROMA**	Foà, Petrucci
70.	**ROMA**	De Fabritiis, Caravita
71.	**ROMA**	Andriani
72.	**ROMA**	Bagnato, Bongarzoni
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74.	**ROMA**	Mangarelli, Pisani
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76.	**ROMA**	Venditti
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78.	**ROMA**	Recine
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86.	**TORINO**	Vitolo, Pregno, Benevolo
87.	**TORINO**	Saglio
88.	**TREVISO**	Gherlinzoni
89.	**TRICASE**	Pavone
90.	**TRIESTE**	Festini, De Sabbata
91.	**UDINE**	Fanin, Patriarca
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