

REGIONE VENETO
AZIENDA U.L.S.S. n. 2
della Marca Trevigiana

con il patrocinio di



SIE
Società Italiana
di Ematologia



HIGHLIGHTS IN EMATOLOGIA

22-23 NOVEMBRE 2019

TREVISO

Sala Convegni
Ospedale Ca' Foncello

Unità Operativa di Ematologia
Responsabile Dott. F. Gherlinzoni

**Real-life:
l'approccio diagnostico-
terapeutico al paziente
ottuagenario**

Nel mieloma multiplo

F. Patriarca (Udine)

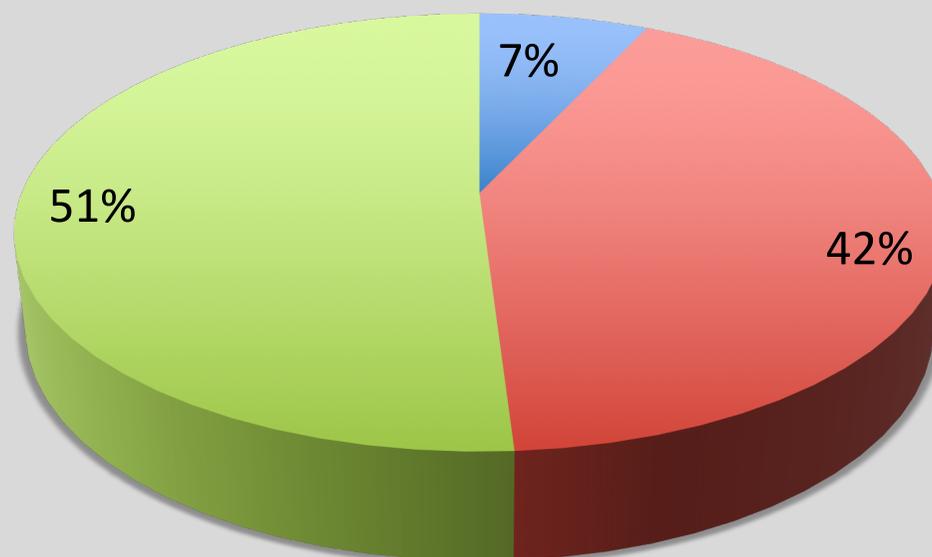
DISCLOSURE 2015-2019

Francesca Patriarca

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Travel and accomodations for congresses
Celgene						X	X
Janssen-Cilag						X	X
Takeda						X	
Biotest							x
Medac							x
Jazz							x



distribuzione per fascia età nel 2015

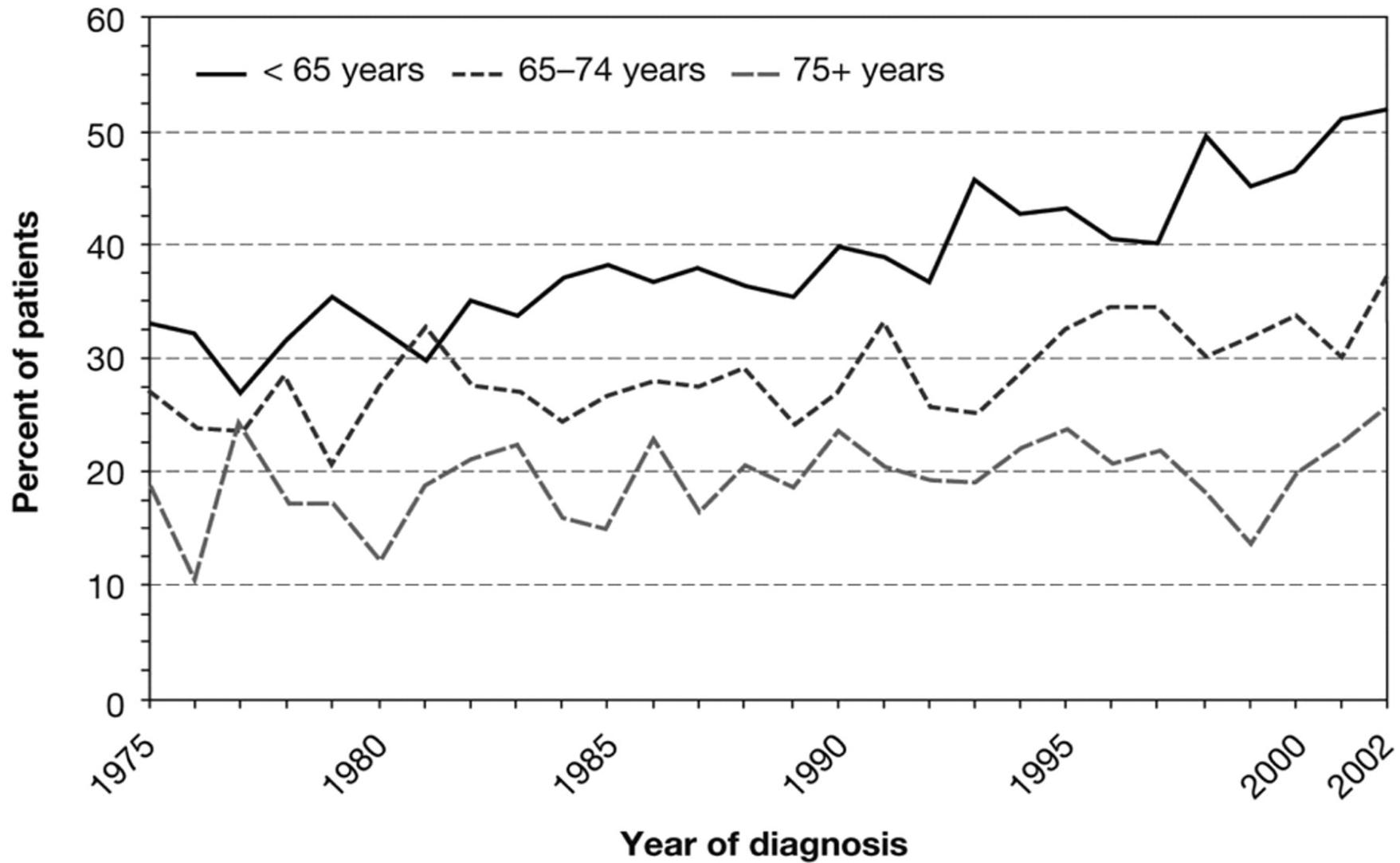


■ 0-49 anni ■ 50-69 anni ■ oltre 70 anni

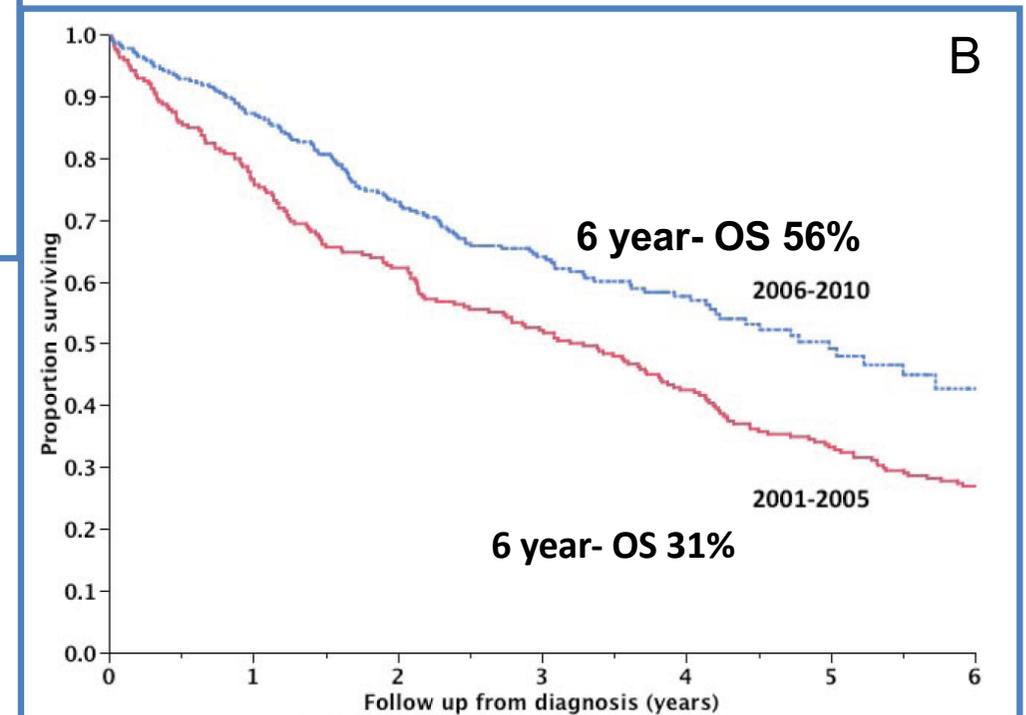
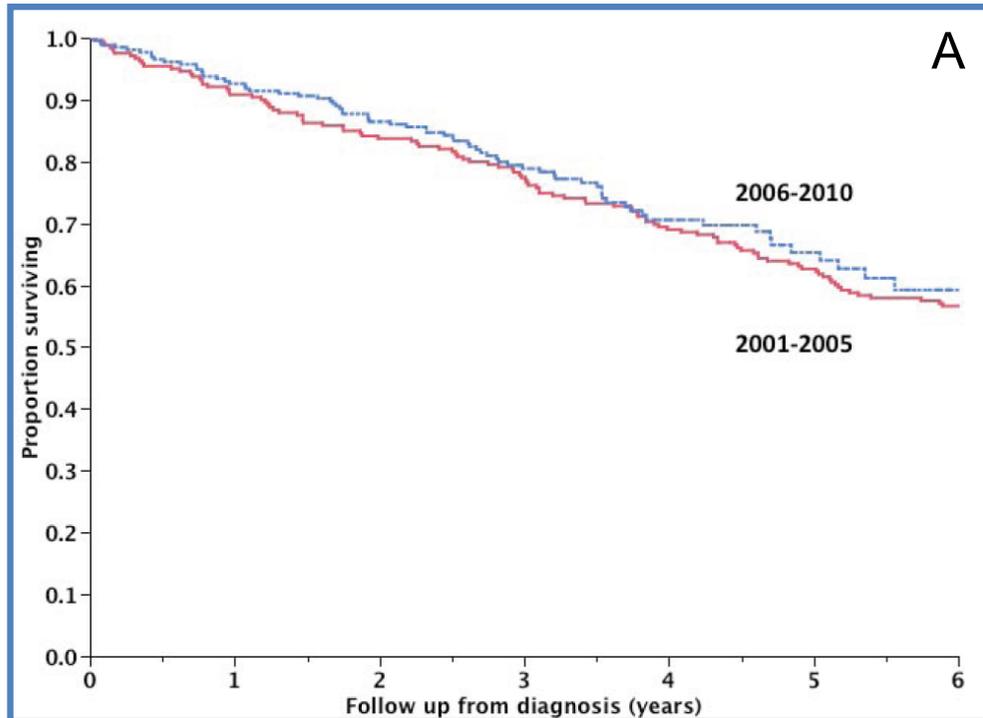
433 casi nel 2015 in Veneto

Nel  picco di incidenza nella fascia di età 80-85 anni (58 casi per 100.000 ab /anno)

Five-year relative survival rates according to the year of diagnosis and the patients' age at diagnosis of multiple myeloma.



Overall survival comparison between patients diagnosed during 2001- 2005 and those diagnosed during 2006-2010 limited to patients < 65 years or younger (panel A) and patients >65 years or old (panel B).



Myeloma features:
cytogenetics,
symptoms, ISS,
prognostic factors

Patients features:
comorbidities
autonomy
VGM
caregiver

Treatment decision in (old) patients

Treatment options:
efficacy
toxicity

Goals of care:
patient expectation
understanding
life expectancy



Chromosome Abnormalities

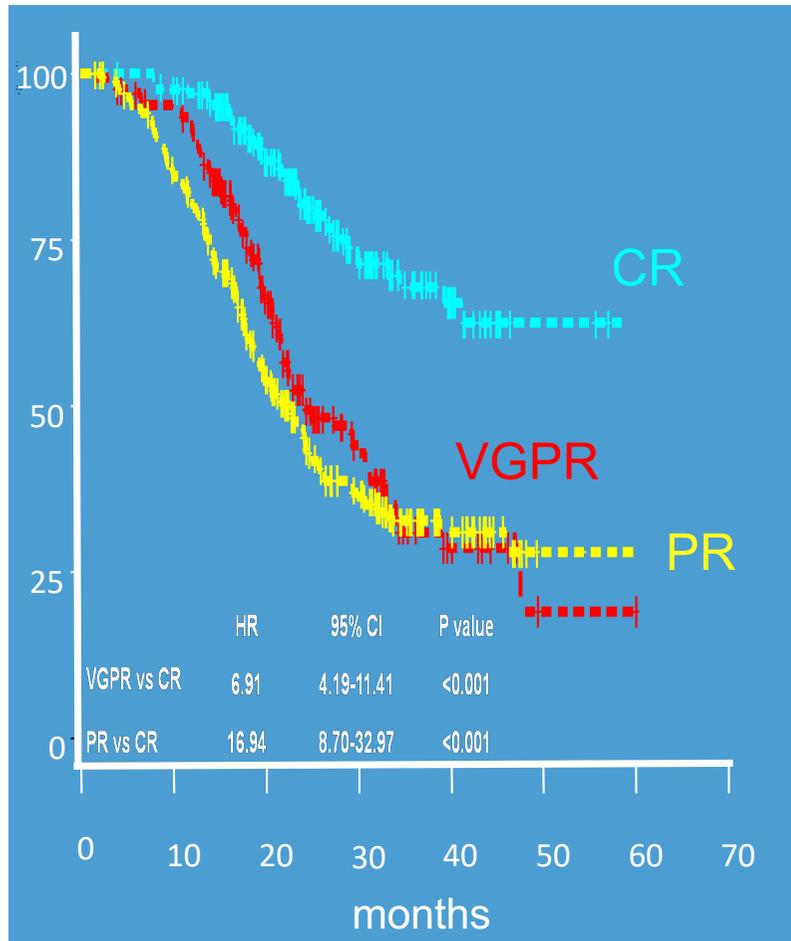
- Medullary samples centrally analyzed by fluorescence in situ hybridation (FISH) : Cytogenetic Unit Pr Avet-Loiseau

	Until 65 y n = 2347	66 – 75 y n = 1239	> 75 y n = 651	p value
Del 13	45%	43.6%	37%	0.004
t (4;14)	14.3%	10.9%	8.3%	<.0001
Del 17p	6%	5.9%	6.1%	NS

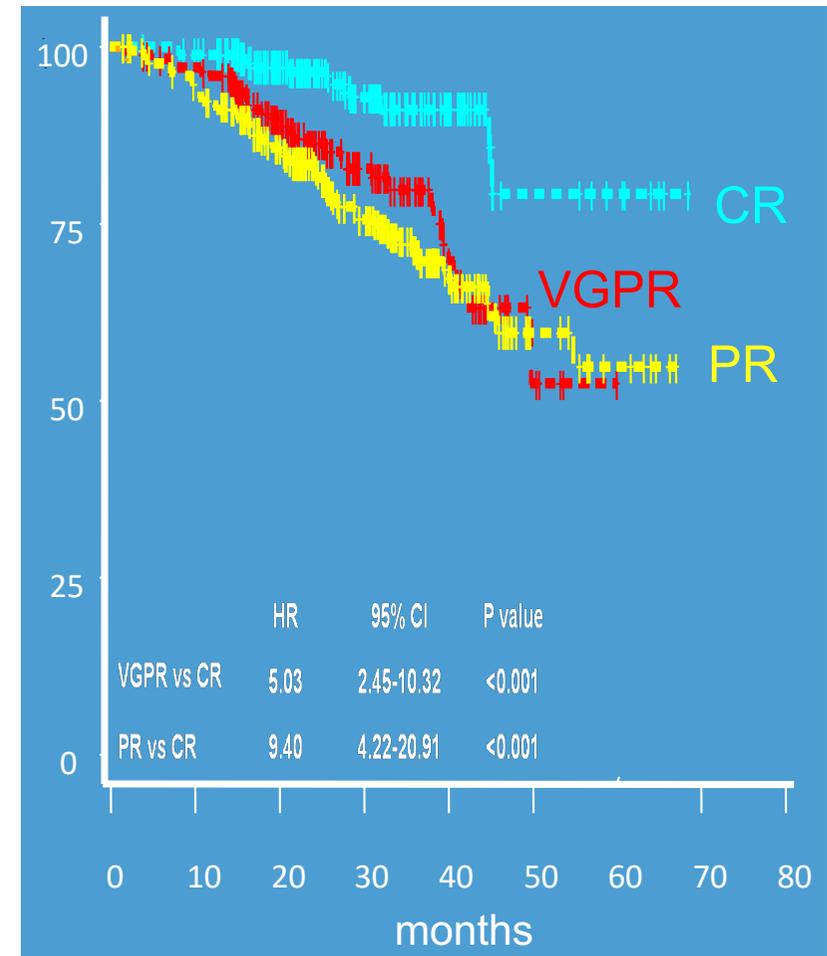
CR predicts long term outcome

Analysis of 1175 elderly patients

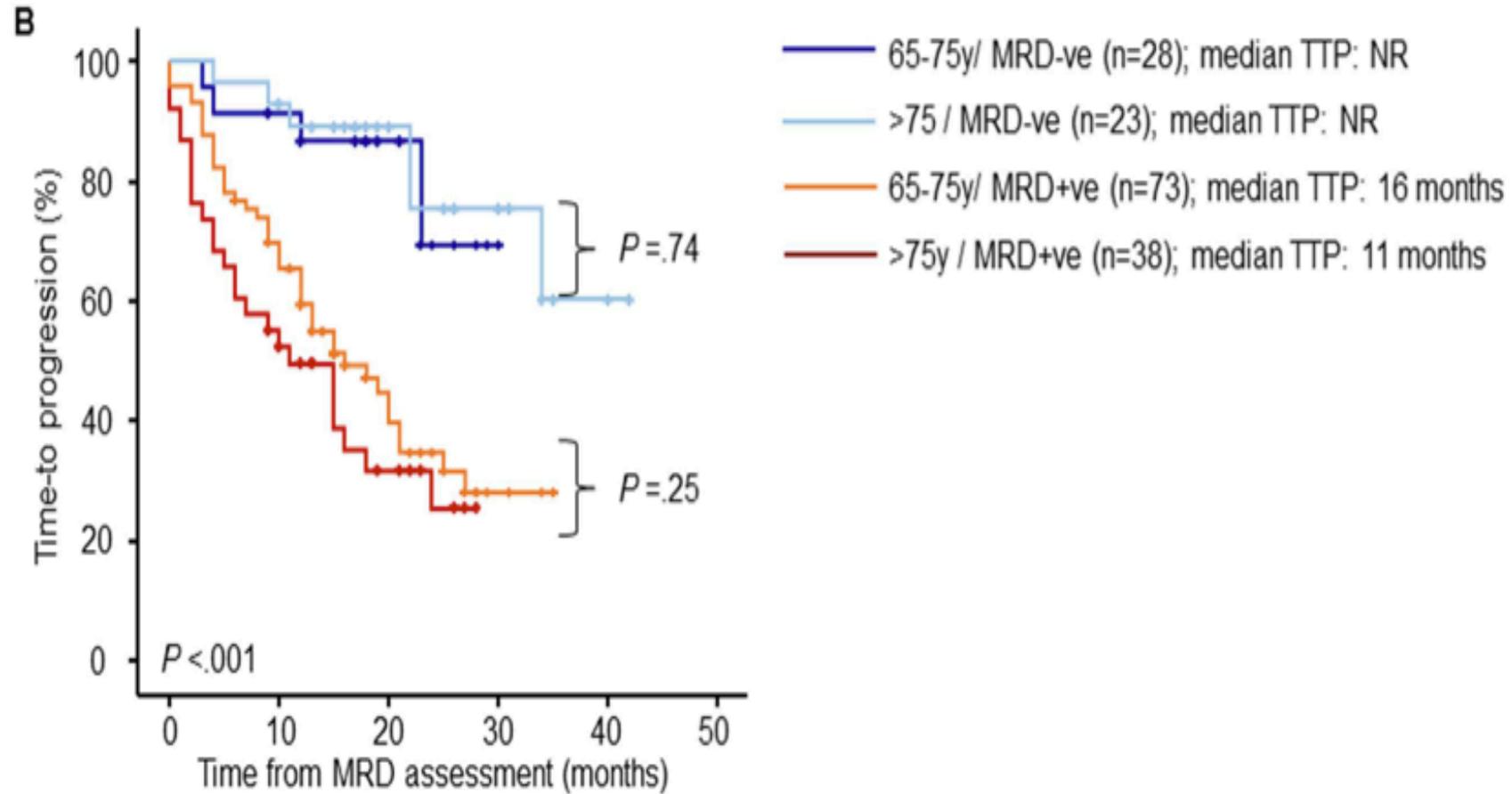
PFS



OS



Impact of reaching MRD negativity on time-to progression according to patients' age (n=162)



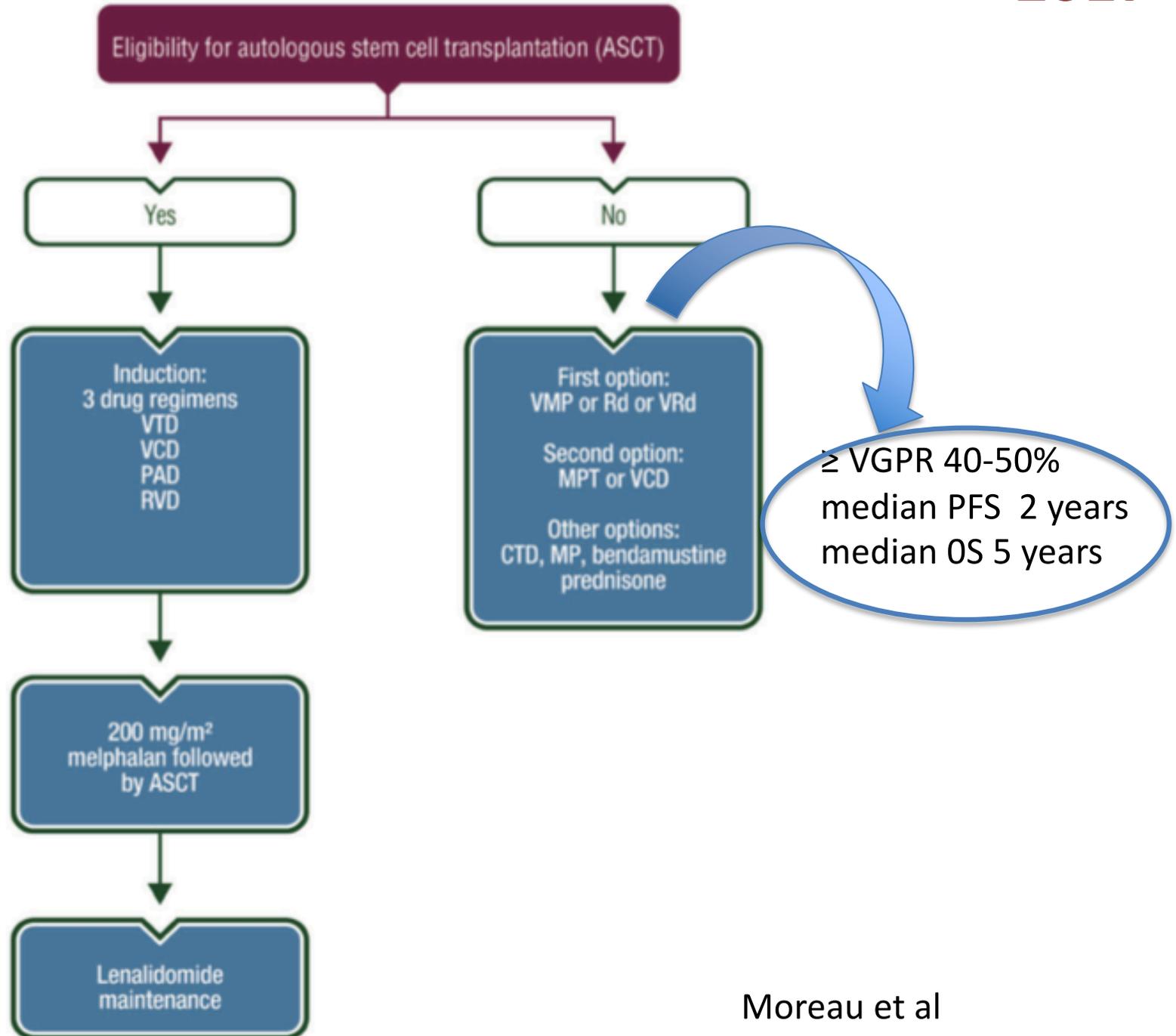
Myeloma features:
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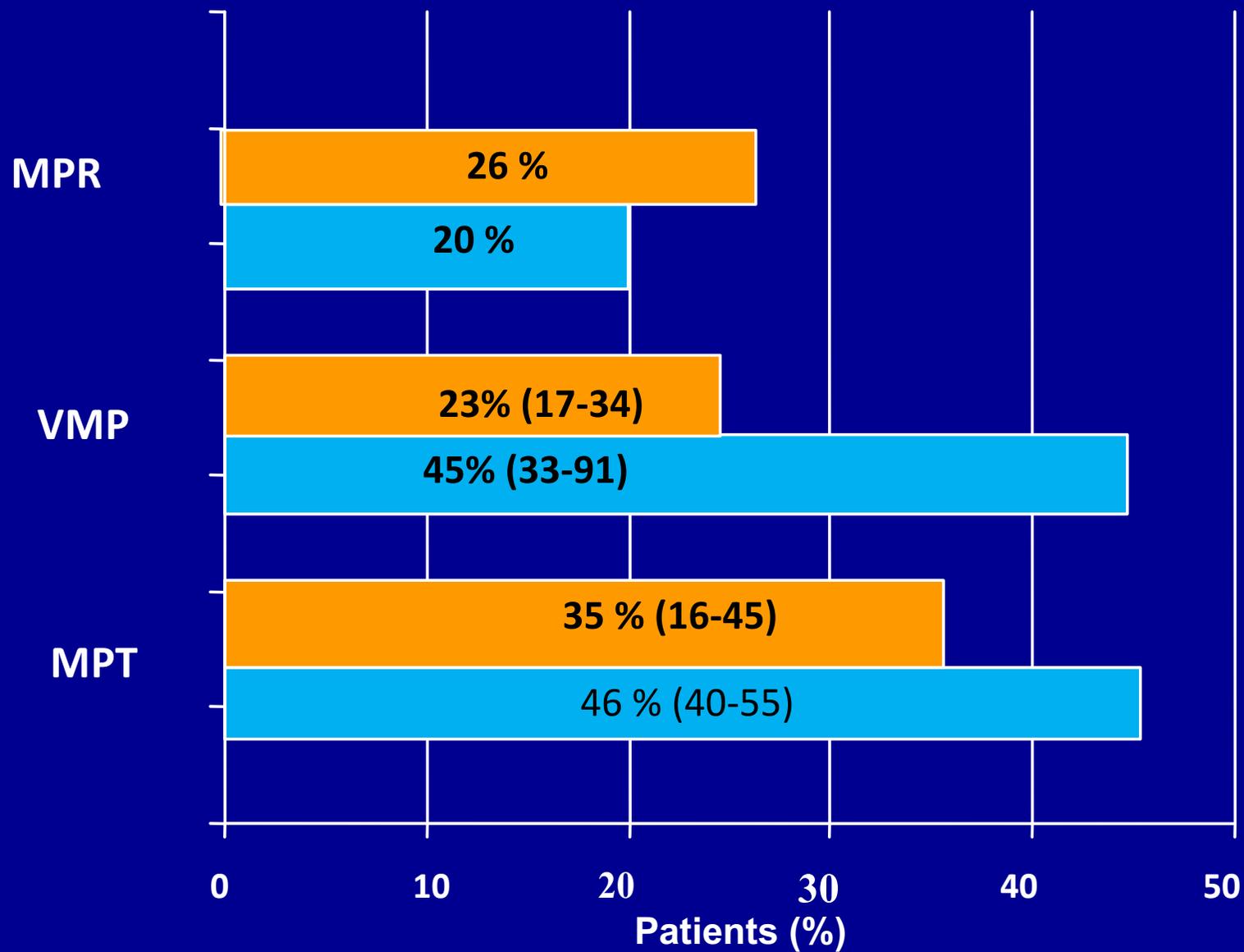
Moreau et al



non-haematol grade 3-5 AE
Neuropathy, cardiac events,
thrombosis, infections



Drop out for AE



OUTCOME OF PATIENTS TREATED WITH FULL-DOSE OR REDUCED-DOSE REGIMENS

author	Any grade 3-5 AE	discontinuation	PFS median	OS%
Standard dose therapies				
VMP Bortezomib 1,4,8,11	91	34	21.7 mo	46% at 5 y
RD Dexa 480 mg /mo	52	27	22.3	78% at 2 y
Lower dose therapies				
VMP Bortezomib 1,8,15,21	51	12-17	24.8 mo	51 % at 5 y
Rd Dexa 160 mg/mo	35	19	26.1 mo	88% at 2 y

Palumbo et al. N Engl J Med 2012;366(19):1759-65
San Miguel et al. N Engl J Med 2008; 359: 906-917

Rajkumar et al, Lancet Oncology 2010;11(1):29-37

GERIATRIC ASSESSMENT

Table 1. Basic ADL scale

Activities
Bathing: Bathes self completely or needs help in bathing only a single part of the body.
Dressing: Gets clothes from closets and drawers and puts on clothes. Some help with tying shoes may be needed.
Toileting: Goes to toilet (may use cane or walker), gets on and off, arranges clothes, cleans genital area without help (may use bedpan/urinal at night).
Transferring: Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.
Continence: Exercises complete self-control over urination and defecation.
Feeding: Gets food from plate into mouth without help. Food may be prepared by another person.

Table 2. IADL scale

Activities
Ability to use telephone
Shopping
Completely unable to shop
Food preparation
Housekeeping
Laundry
Mode of transportation
Travels independently on public transportation or drives own car
Responsibility for own medications
Ability to handle finances

Table 3. Charlson Comorbidity Index

Comorbidity
Myocardial infarction
Congestive heart failure
Peripheral vascular disease
Cerebrovascular disease
Dementia
Chronic pulmonary disease
Connective tissue disease
Ulcer
Mild liver disease
Diabetes
Diabetes with end-organ damage
Ictus
Moderate-to-severe renal failure
Nonmetastatic solid tumor
Leukemia
Lymphoma, MM
Moderate-to-severe liver disease
Metastatic solid tumor
AIDS

Table 4. GA to identify frail patients with MM

Age, y	GA
>80	
76-80	Plus at least 1 of the following: ADL score ≤ 4 IADL score ≤ 5 CCI score ≥ 2
≤ 75	Plus at least 2 of the following: ADL score ≤ 4 IADL score ≤ 5 CCI score ≥ 2

The GA score can be calculated through the Web site <http://www.myelomafrailltyscorecalculator.net>.

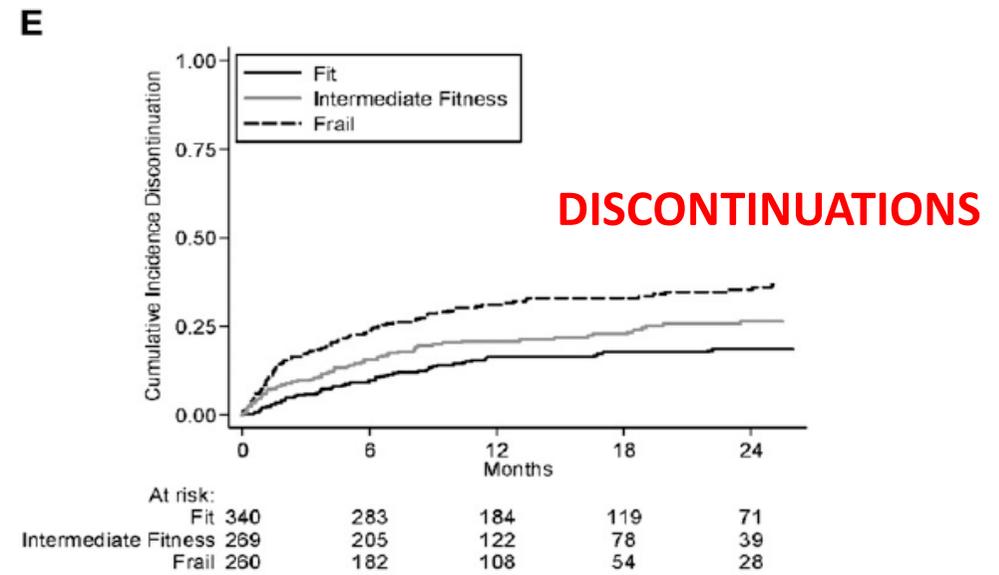
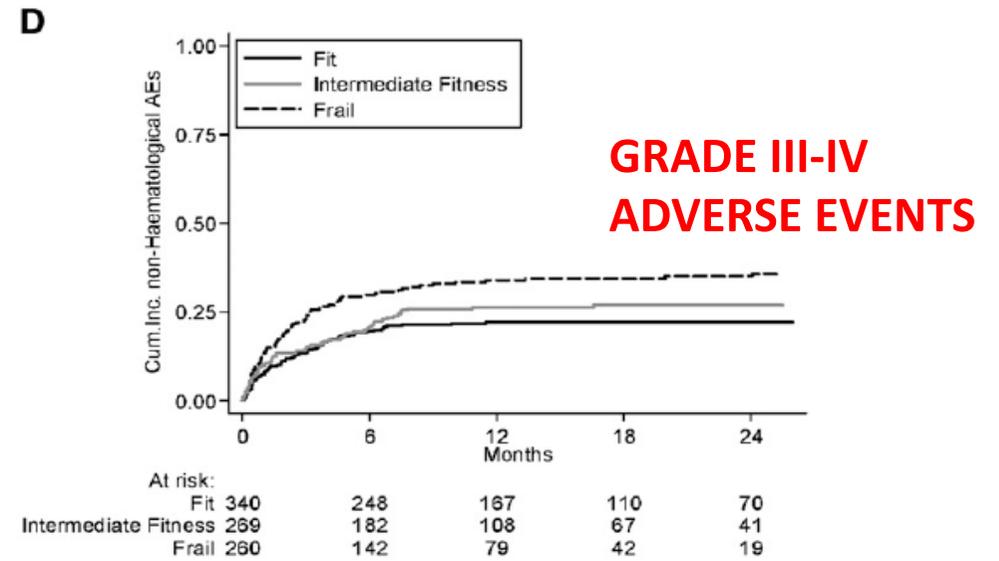
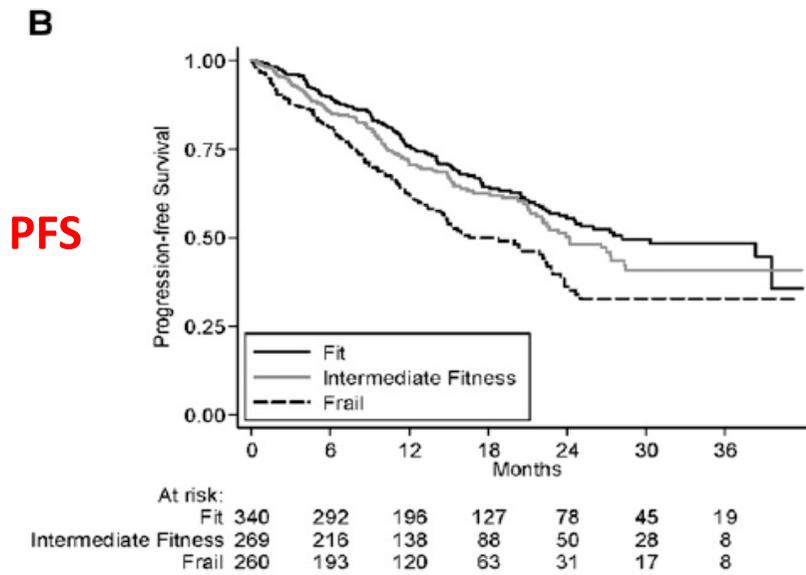
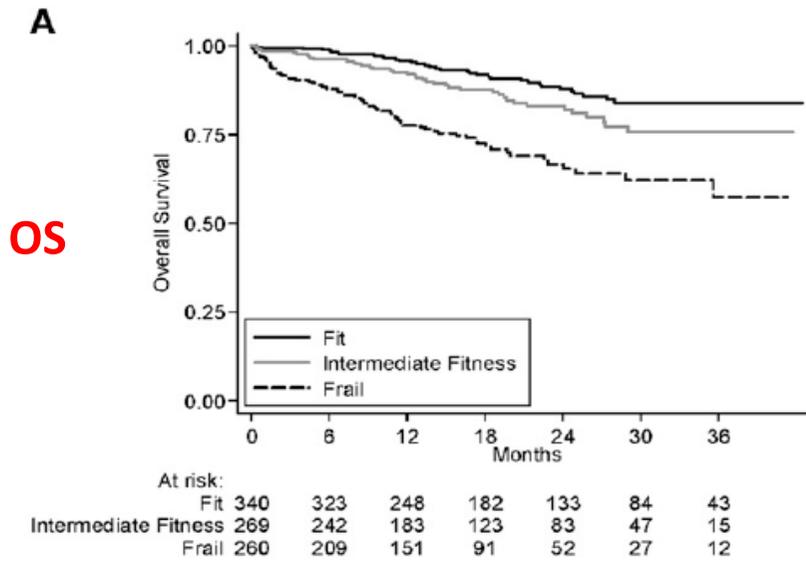
**How I treat fragile MM
Larocca & Palumbo
Blood Nov 2015**



**INADEGUATE
DEFINITION
OF VGM**



Relationship between fitness and clinical outcomes



EMN-01 Study Design

1°
R
A
N
D
O
M
I
Z
A
T
I
O
N

Rd¹
Nine 28-day courses
R: 25 mg, d 1-21
d: 40 mg, d 1,8,15,22

M²PR
Nine 28-day courses
M: 0.18 mg/kg, d 1-4
P: 1.5 mg/kg, d 1-4
R: 10 mg, d1-21

C³PR
Nine 28-day courses
C: 50 mg, d1-21
P: 25 mg, 3 times wk
R: 25 mg, d1-21

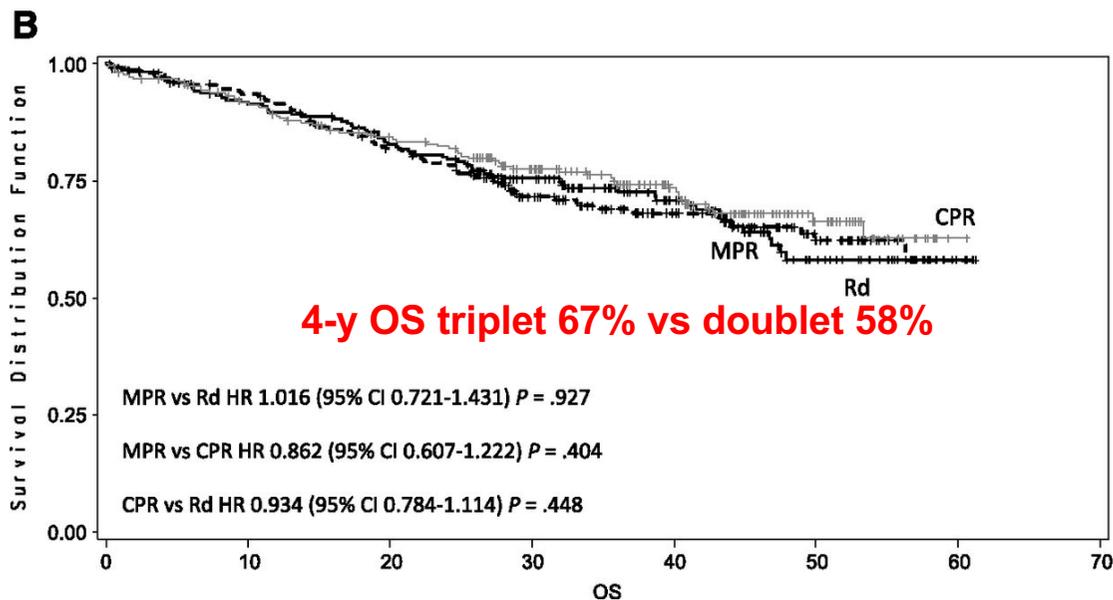
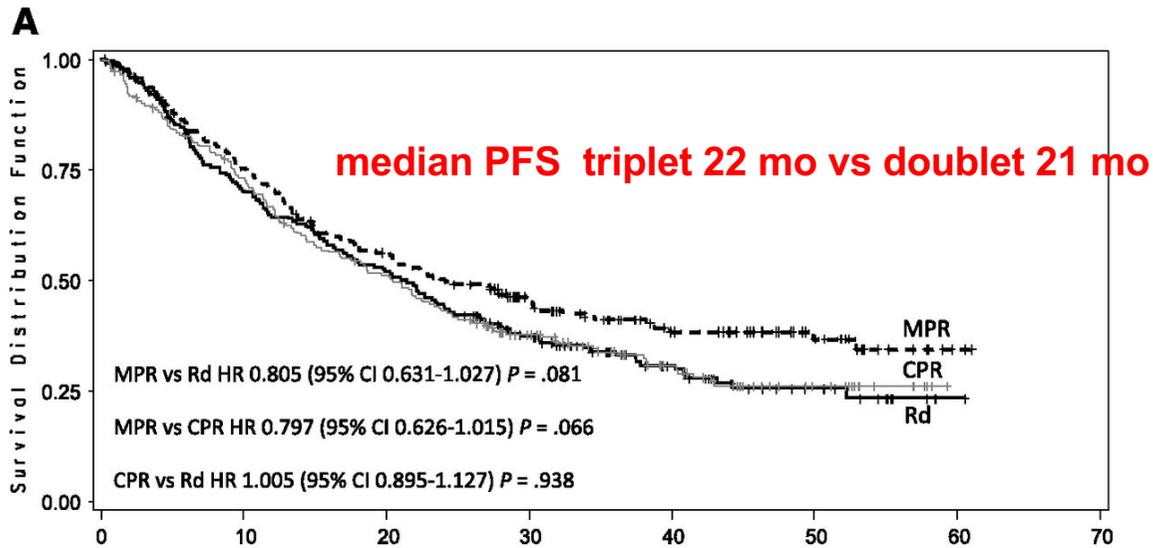
2°
R
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MAINTENANCE
28-day courses until relapse
R: 10 mg/day, days 1-21

MAINTENANCE
28-day course until relapse
R: 10 mg/day, days 1-21
P: 25 mg; 3 times wk

**75 years: ¹Dexamethasone 20 mg/week; ²Melphalan 0.13 mg/Kg;
³Cyclophosphamide: 50 mg one day on**

R, Lenalidomide; d, low dose dexamethasone; C, cyclophosphamide; M, melphalan; P, prednisone



(median follow up 39 mesi)

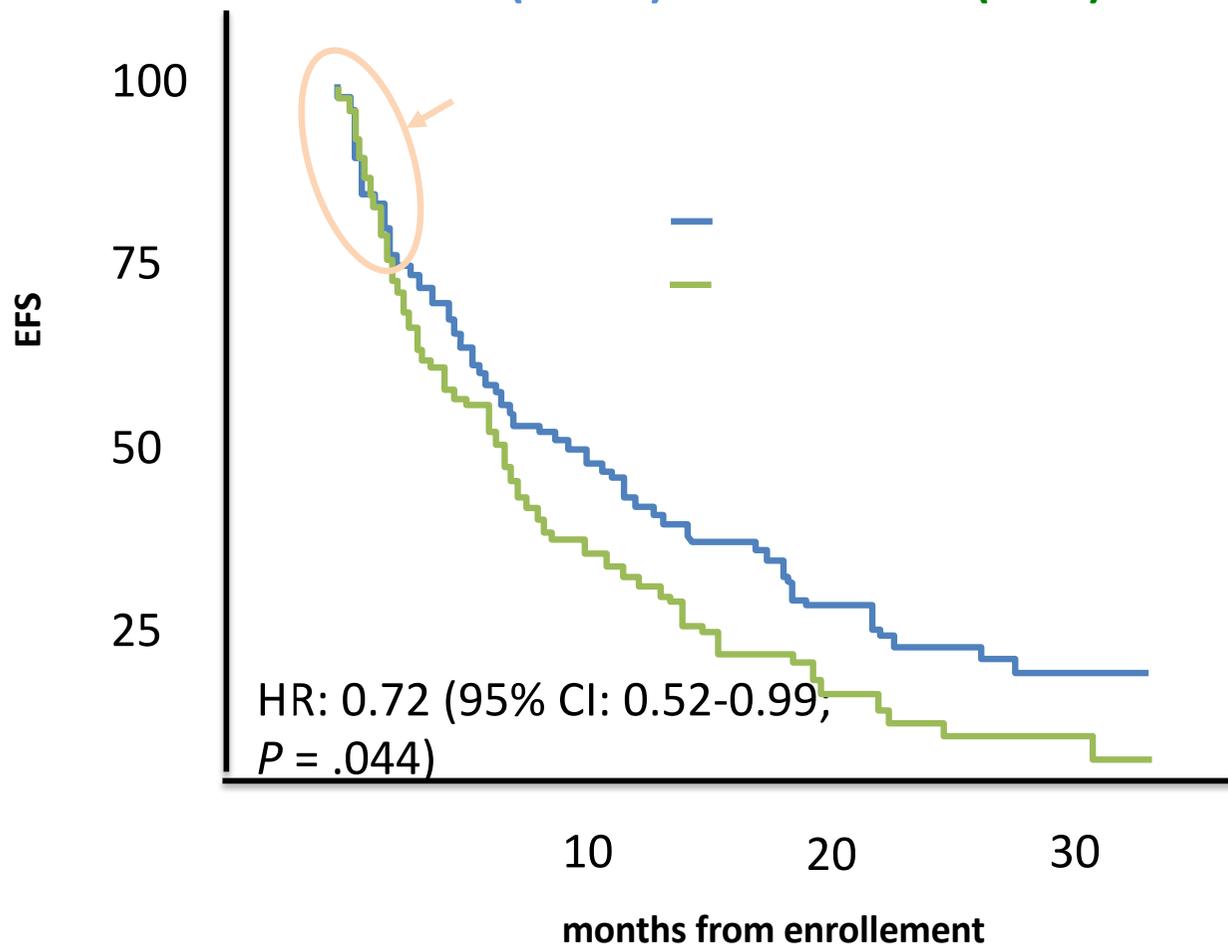
At least one grade > 3 grade hematological event was 29% of RD, 32% of CPR and 68% of MPR

Key Points

- Triplet lenalidomide-based regimens did not induce any advantage over doublet lenalidomide-based regimens in elderly myeloma patients.

Rd-R vs Continuous Rd in Intermediate-Fit Elderly Pts: Event-Free Survival (Primary Endpoint)

- Multicenter, randomized, controlled phase III trial of Rd induction followed by R maintenance at 10/day vs Continuous Rd at 25 /day median EFS: Rd-R (n.101) 9.3 mo vs Rd (n.98) 6.6 mo



9% discontinued study < 60 days from start of therapy, due to

- Toxicity: 4.5%
- Toxic death: 1.5%
- Decline in condition or lost to follow-up: 1.5%
- PD: 0.5%
- Death not related to MM: 1%

- Similar EFS observed for patients deemed intermediate-fit due to age or geriatric assessment

FRAILITY STATUS

Table 3 Frailty status definition and related treatment goals in elderly NDMM patients

IMWG-FRAILITY INDEX: Age, CCI, ADL, IADL		
FIT	INTERMEDIATE	FRAIL
0	1	2-5
IMWG-frailty index points	IMWG-frailty index point	IMWG-frailty index points
<i>CCI ≥ 2: 1</i>		
<i>IADL < 5: 1</i>		
<i>ADL < 4: 1</i>		
<i>Age 76–80: 1, > 80: 2</i>		
REVISED MYELOMA COMORBIDITY INDEX (R-MCI): Age, KPS, renal function, lung function, frailty ± cytogenetics		
FIT	INTERMEDIATE	FRAIL
0–3	4–6	7–9
R-MCI points	R-MCI points	R-MCI points
<i>Age 60–69: 1, ≥ 70: 2</i>		
<i>KPS: 80–90%: 2, < 70%: 3</i>		
<i>Renal disease: eGFR < 60: 1</i>		
<i>Lung disease: moderate/severe: 1</i>		
<i>Frailty: moderate or severe: 1 ± cytogenetics: unfavorable: 1</i>		
MAYO FRAILITY INDEX: Age, ECOG PS, NT-proBNP		
STAGE I	STAGE II/ STAGE III	STAGE IV
0	1 (STAGE II)	3
Mayo frailty index points	Mayo frailty index point	Mayo frailty index points
	2 (STAGE III)	
	Mayo frailty index points	
<i>Age ≥ 70: 1</i>		
<i>ECOG PS ≥ 2: 1</i>		
<i>NT-proBNP ≥ 300 ng/L: 1</i>		

The clinical impact of frailty in transplant ineligible patients with multiple myeloma treated with bortezomib-based chemotherapy as front line therapy

AIM: comparison between 2 frailty scores

METHODS : retrospective data collection of 411 patients with a median age of 79 years with MM at 6 university hospitals in South Korea between December 2012 and Oct 2017. All patients have been treated with bortezomib, melphalan and prednisone (VMP) as a first-line treatment.

	IMWG*	2y-PFS	2y-OS	R-MCI	2y-PFS	2y-OS
fit	21%	62%	89%	38%	68%	90%
Intermediate	35%	62%	87%	49%	53%	86%
frail	44%	42%	77%	13%	14%	52%

*ADL and IADL replaced with ECOG

Conclusions:

Frail patients showed a significant short survival in PFS and OS compared to fit patients. However, prospective data and new frailty score are needed

FRAILTY STATUS: RECOMMENDATIONS

“Less toxic for frail” drugs
“Frail” drugs/regimens

GOAL OF TREATMENT

FIT

Efficacy: deep response

INTERMEDIATE

Balance efficacy and toxicity

FRAIL

Conservative approach, low toxicity

TREATMENT

Full-dose therapy

ASCT
TRIPLET REGIMENS
VMP
VRD
DOUBLET REGIMENS
Rd

Full- or reduced-dose therapy

DOUBLET REGIMENS
Rd
Vd
Reduced-dose triplet

Reduced dose therapy

REDUCED-DOSE
DOUBLET REGIMENS
rd
Vd
Palliative + supportive care



MYELOMA THERAPY^{a-c,e-g,i,j}

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES

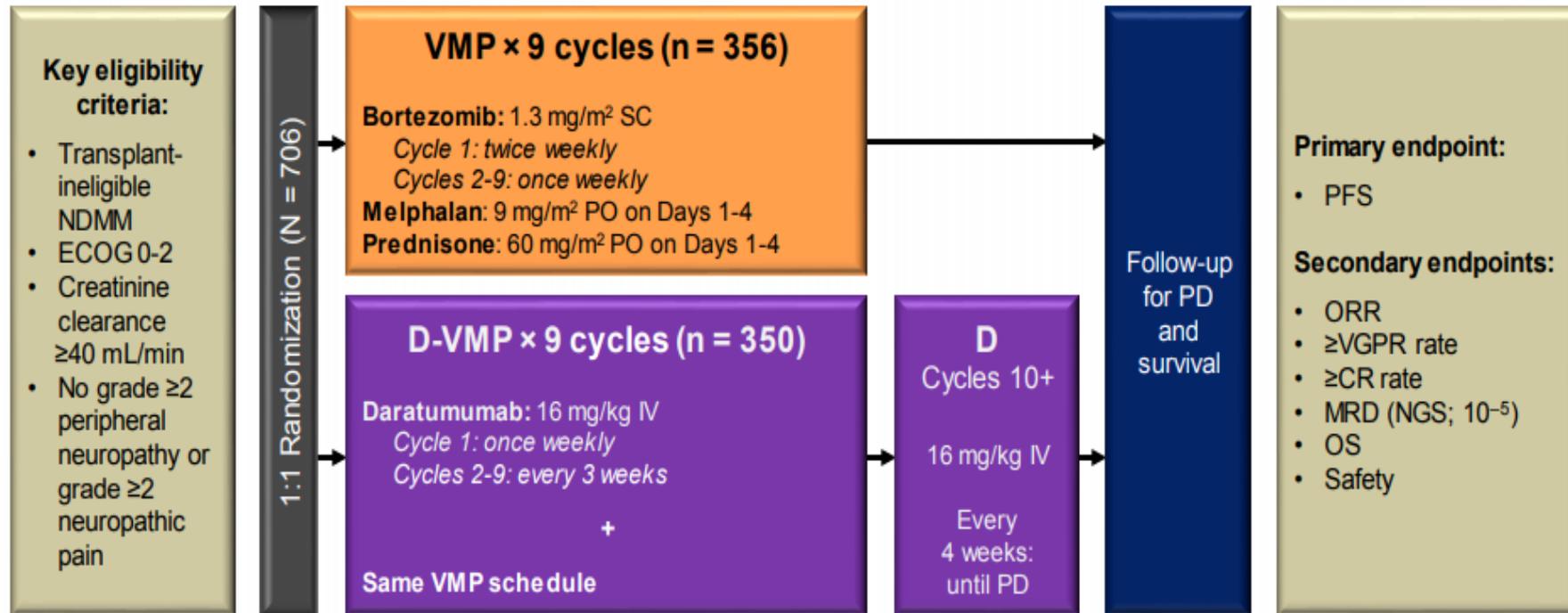
Preferred Regimens

- Bortezomib/lenalidomide/dexamethasone (category 1)^o
- Daratumumab^P/lenalidomide/dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)^{k,q}
- Bortezomib/cyclophosphamide/dexamethasoneⁿ

Other Recommended Regimens

- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone
- Daratumumab^P/bortezomib/melphalan/prednisone (category 1)

Alcyone: study design



Stratification factors

- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥ 75 years)

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

Statistical analyses

- 360 PFS events: 85% power for 8-month PFS improvement^a

356 patients

≥ 75 y: 30%

ECOG 0-1: 80%

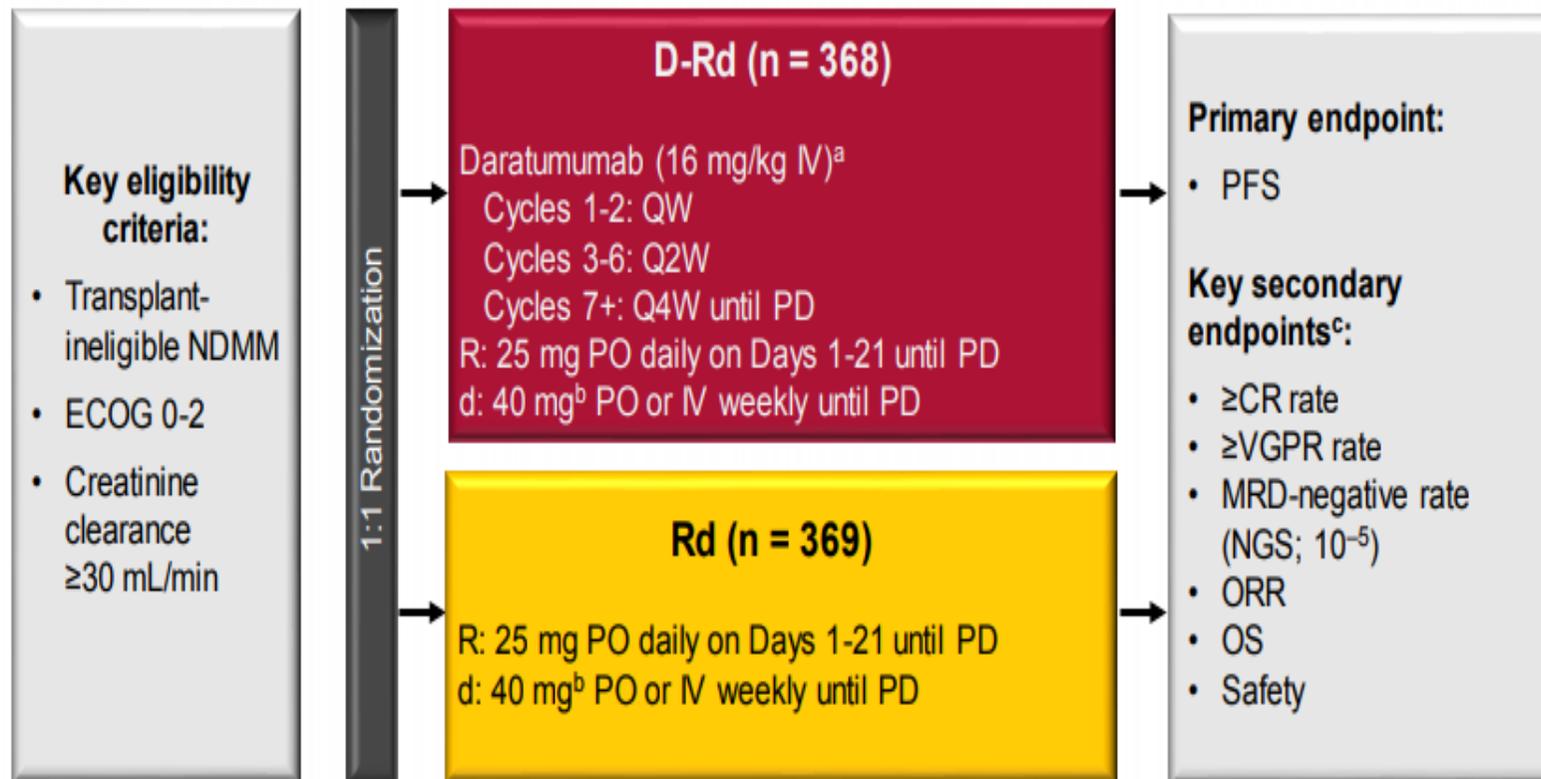
Standard risk cyto: 84%

Mateos et al. N E J M 2018

Dimopoulos et al. Oral presentation 156 ASH 2018

Maia: study design

- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)



Stratification factors

- ISS (I vs II vs III)
- Region (NA vs other)
- Age (<75 vs ≥ 75 years)

Cycle: 28 days

^aOn days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.

^bFor patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.

^cEfficacy endpoints were sequentially tested in the order shown.

737 patients

≥ 75 y: 44%

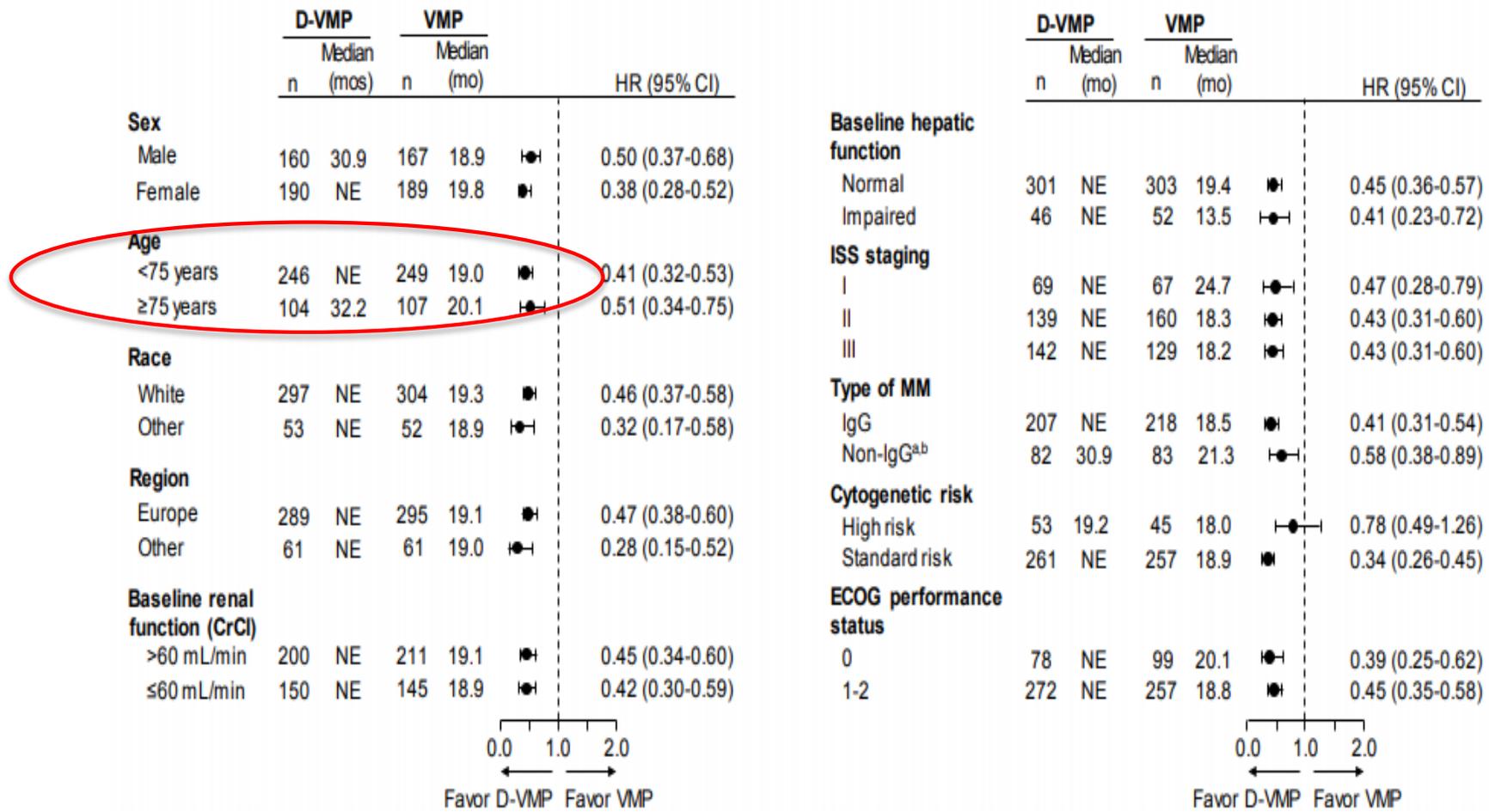
ECOG0-1: 84%

Standard risk cyto :86%

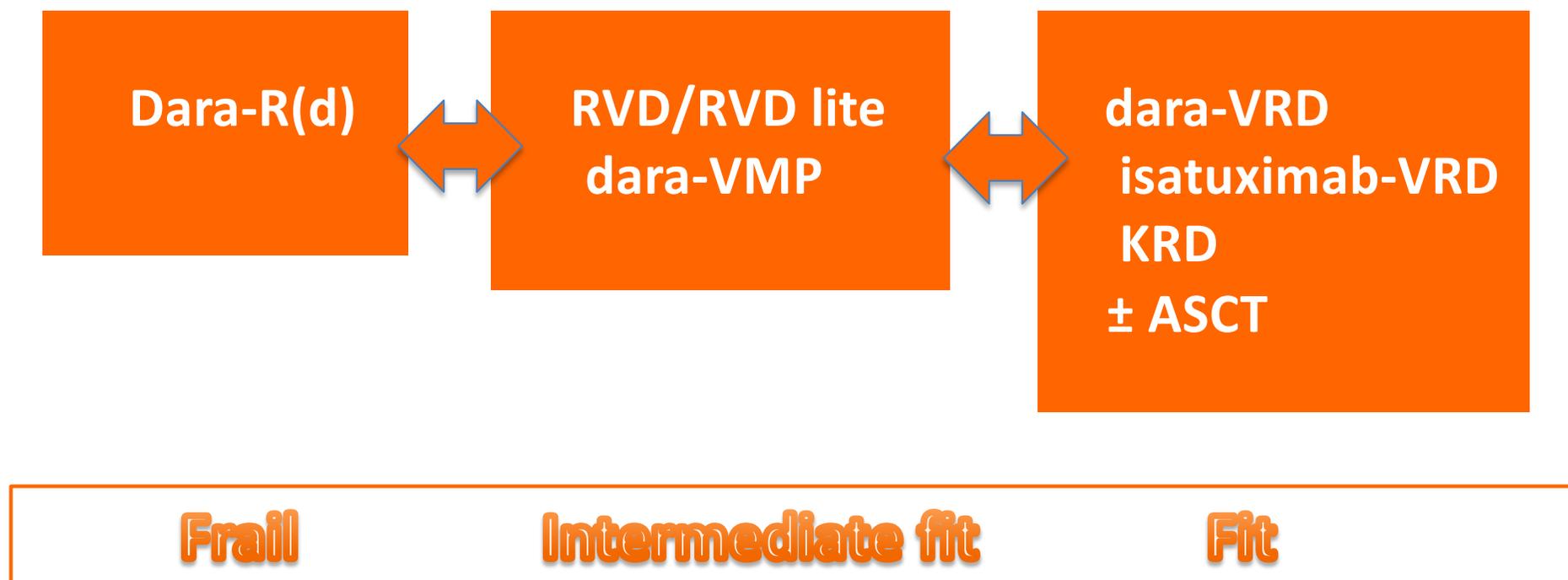
OUTCOME OF NEW STANDARDS

	Original RVd	Lite RVd	Dara-VMP	Dara-RD
Study name/author	Durie 2017	O'Donnell 2018	Alcyone	Maia
Phase	RVd vs Rd	Phase 2	Dara-VMP vs VMP	Dara-Rd vs Rd
N° pts	525	53	356	737
Median age	63 y	73 y	71 y	73 y
OR (CR)	82% (16%)	86% (44%)	91% (45%)	93 % (48%)
PFS	43 mo	35 mo	60% at 30 mo	71% at 30 mo
OS	75 mo	NR at 30 mo	NR at 30 mo	NR at 30 mo
Extrahematotoxicity	Higher neuropathy in RVd arm	3-4 WHO neuropathy 3%	Similar in both arms	Similar in both arms

PFS in Prespecified Subgroups



PROPOSAL



CONCLUSIONS

- ◆ Frailty score recognized by the haematology community are urgent.
- ◆ New standards will enter clinical practice, placing beside the old combinations.
- ◆ “Frail drugs/regimens” should be confirmed by real word data and patients reported outcome.

A PHASE 2 STUDY WITH 3 LOW INTENSITY BORTEZOMIB REGIMENS

1°
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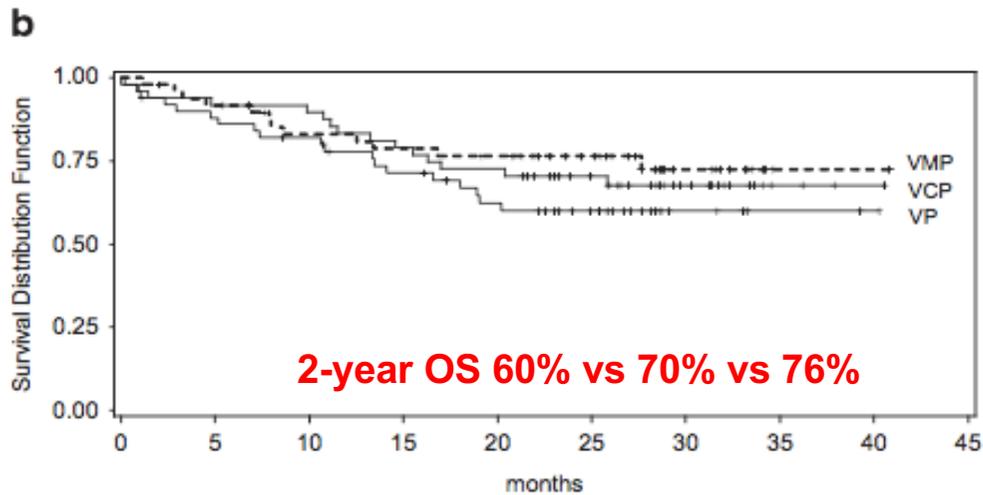
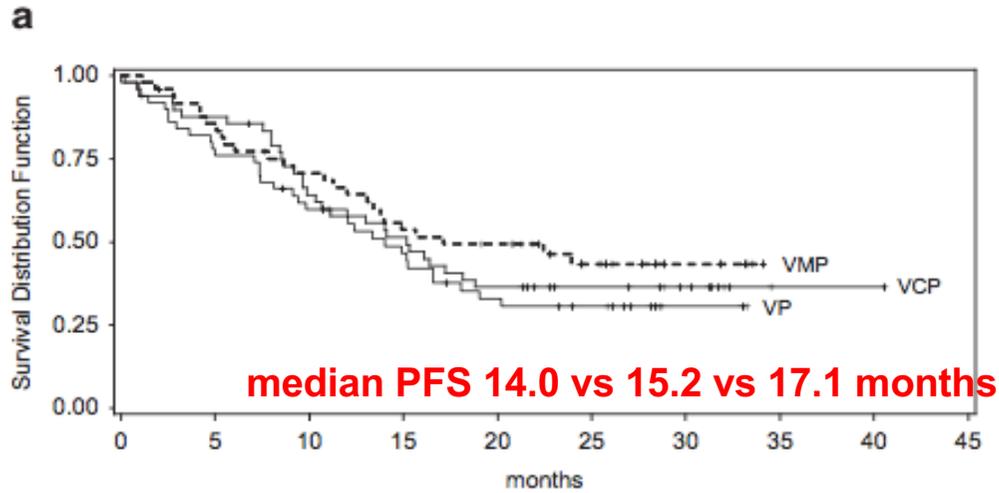
VP
Nine 28-day courses
V: 1,3 mg/mq, d 1,8,15,22
P: 50 mg, every other day

VCP
Nine 28-day courses
V: 1,3 mg/mq, d 1,8,15,22
P: 50 mg, every other day
C: 50 mg, every other day

VMP
Nine 28-day courses
V: 1,3 mg/mq, d 1,8,15,22
P: 50 mg, every other day
M: 2 mg, every other day



Maintenance until relapse
V: 1,3 mg/mq, d 1,15



Fit

16%

**Intermediate
Fitness**

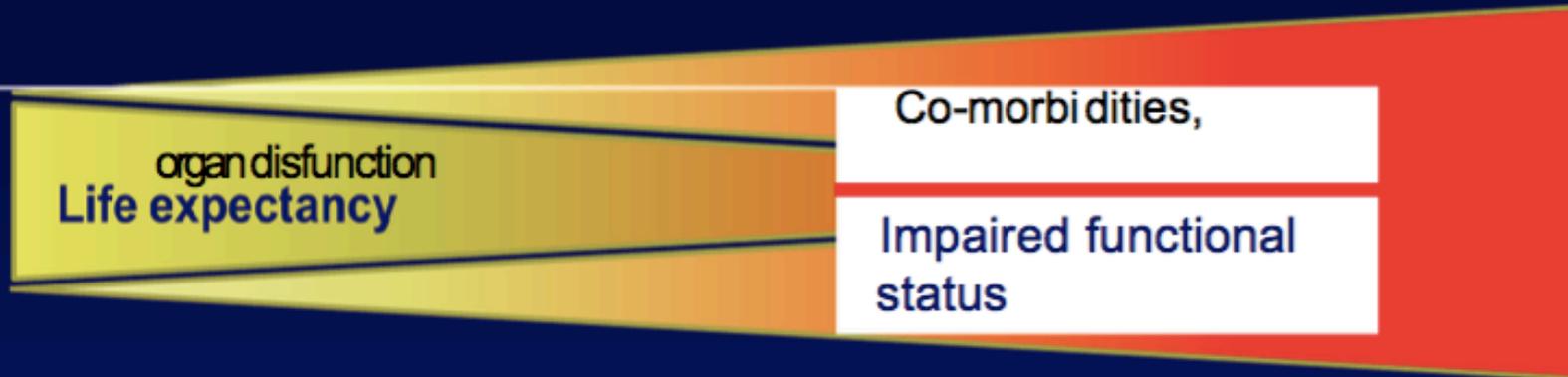
30%

Frail

54%

discontinuation rate for AEs was 12% of VP, 14% of VCP and 20% of VMP

Treatment goals in elderly MM patients



Deep remission

Goal

CR/MRD-negativity

Priority

Efficacy



Balance efficacy/safety

Good response

Combination of efficacy/safety



Do not harm

QoL

Low toxicity

Treatment Decision in Older Patients

Patients

- ADL
- IADL
- Comorbidities
- Hospitalization
- Medications
- Social Support

Multiple Myeloma

- Cytogenetics
- Stage
- Tumor burden
- Optimal Chemo
- Supportive meds

Goals of Care (CR vs Disease Control?)

Expectations

Understanding

Life Expectancy

PERSONALIZED THERAPY ACCORDING TO AGE AND VULNERABILITY

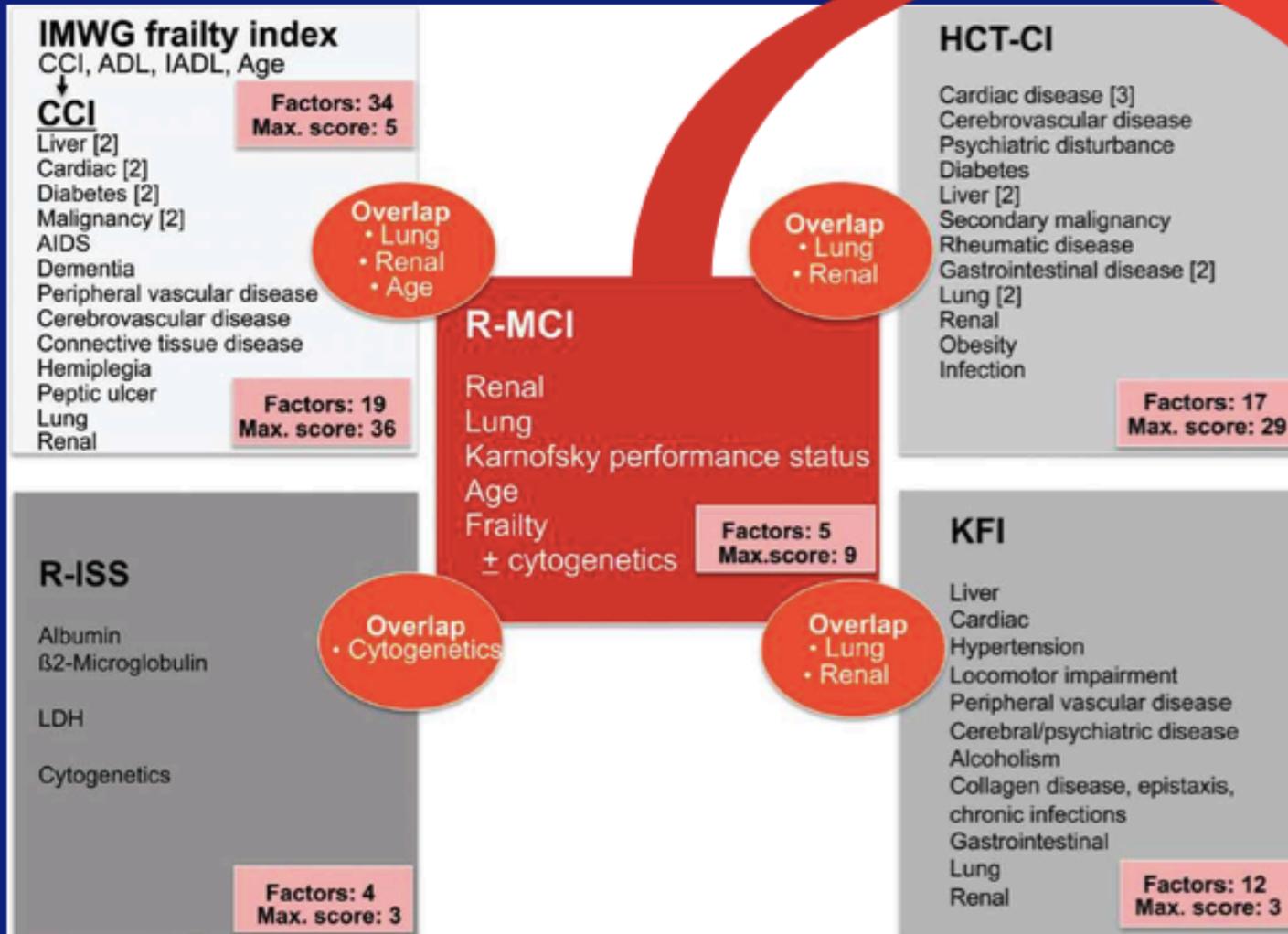
agent	FIT patients Level 0	UNFIT patients Level -1	FRAIL patients Level -2
thalidomide	100 mg/d	50 mg/d	50 mg/qod
Lemalidomide	25 mg/d 1-21	15 mg/d 1-21	10 mg/d 1-21
Bortezomib	1,3 mg/mq 1,4,8,11	1,3 mg/mq 1,8,15,21	1,0 mg/mq 1,8,15,21
Dexamethasone	160 mg/4w	80 mg/4w	40 mg/4w
prednisone	60 mg/mq 1-4	30 mg/mq 1-4	15 mg/mq 1-4
melphalan	0.25 mg/Kg 1-4	0.18 mg/Kg 1-4	0.13 mg/Kg 1-4
cyclophosphamide	100 mg/d	50 mg/d	50 mg/qod

R-MCI

I-MCI

Variables	Mild Moderate	Definition and grading	Severe
1. Renal function: eGFR / serum creatinine	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4
2. Lung function: dyspnea or FEV/FVC, FEV ₁ , TLC, respiratory insufficiency	dyspnea upon intense activity, mildly altered lung function	dyspnea upon moderate activity, moderately altered lung function or respiratory insufficiency	dyspnea at rest/few steps taken/the need for oxygen/non-invasive ventilation or FEV ₁ <50%
3. Karnofsky Performance Status	90%	80%	≤70%
4. Cardiac function: arrhythmias, myocardial infarction/CAD, heart failure	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4
5. Hepatic function: chronic hepatitis, cirrhosis, fibrosis, hyperbilirubinemia	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4
6. GI disease: nausea, vomiting, diarrhea, ulcer	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3
7. Disability: help in personal care and household tasks	occasional	frequent	≥1x/day
8. Frailty: weakness, poor endurance, low physical activity, slow gait speed	1 factor	2 factors	≥3 factors
9. Infection	local intervention	oral intervention	iv. intervention
10. Thromboembolic event	venous thrombosis	thrombosis, medical intervention indicated	life-threatening, urgent intervention indicated
11. PNP	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4
12. Pain	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4
13. Secondary malignancy	1. chronological criteria: before, synchronous or after MM 2. local criteria: local vs. disseminated cancer 3. etiological criteria: hematological, solid or skin tumors		

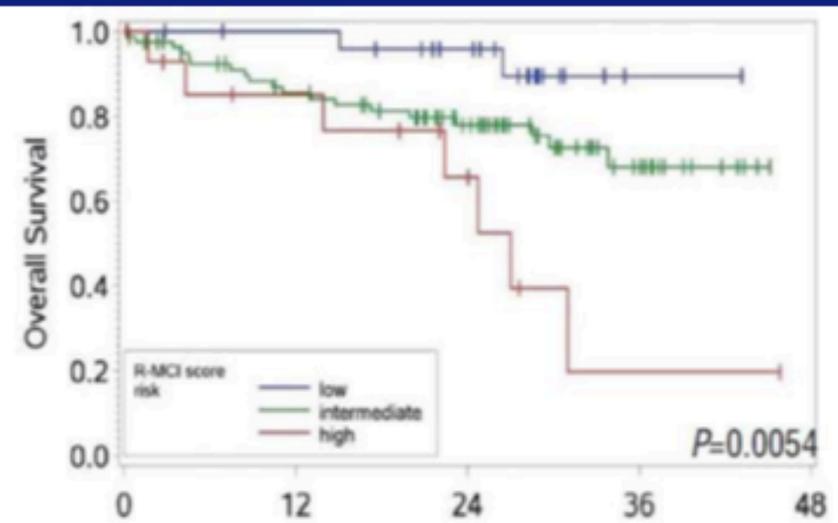
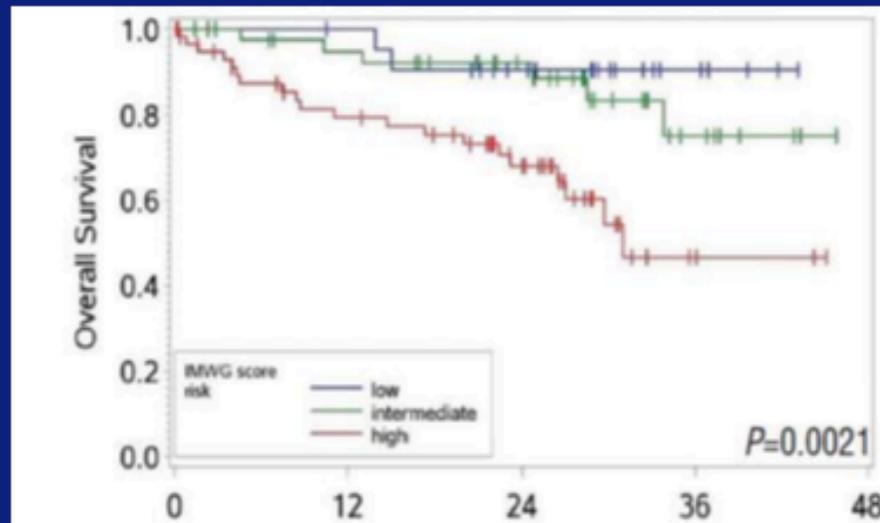
R-MCI



FIT ≤ 3
Intermediate 4-6
Frail >6

Geriatric assessment in multiple myeloma patients: validation of the International Myeloma Working Group (IMWG) score and comparison with other common comorbidity scores

Monika Engelhardt,¹ Sandra Maria Dold,¹ Gabriele Ihorst,² Alexander Zober,³ Mandy Möller,¹ Heike Reinhardt,¹ Stefanie Hieke,³ Martin Schumacher,² and Ralph Wäsch¹



<http://www.myelomacomorbidityindex.org>