



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

**Nel mieloma multiplo**

*F. Patriarca (Udine)*

# DISCLOSURE 2015-2019

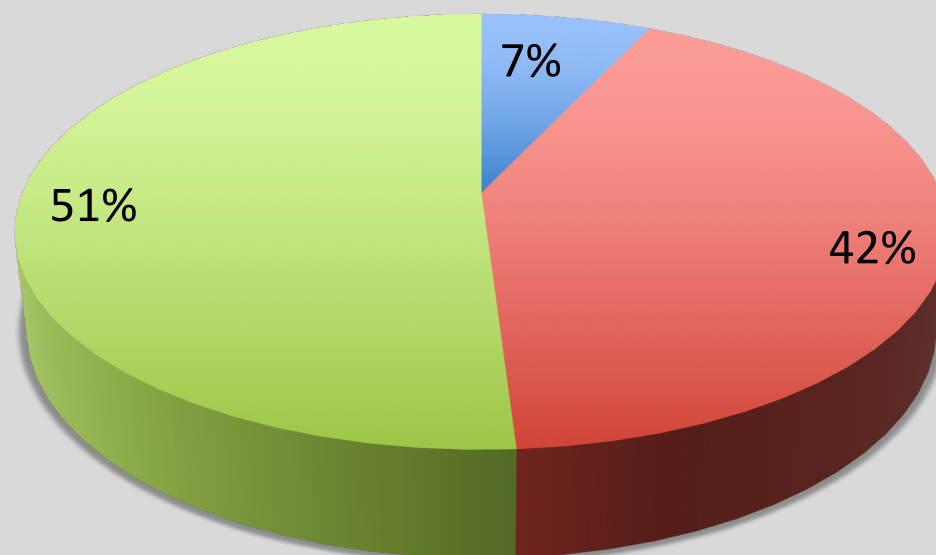
Francesca Patriarca

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



Registro  
Tumori  
Veneto

### distribuzione per fascia età nel 2015

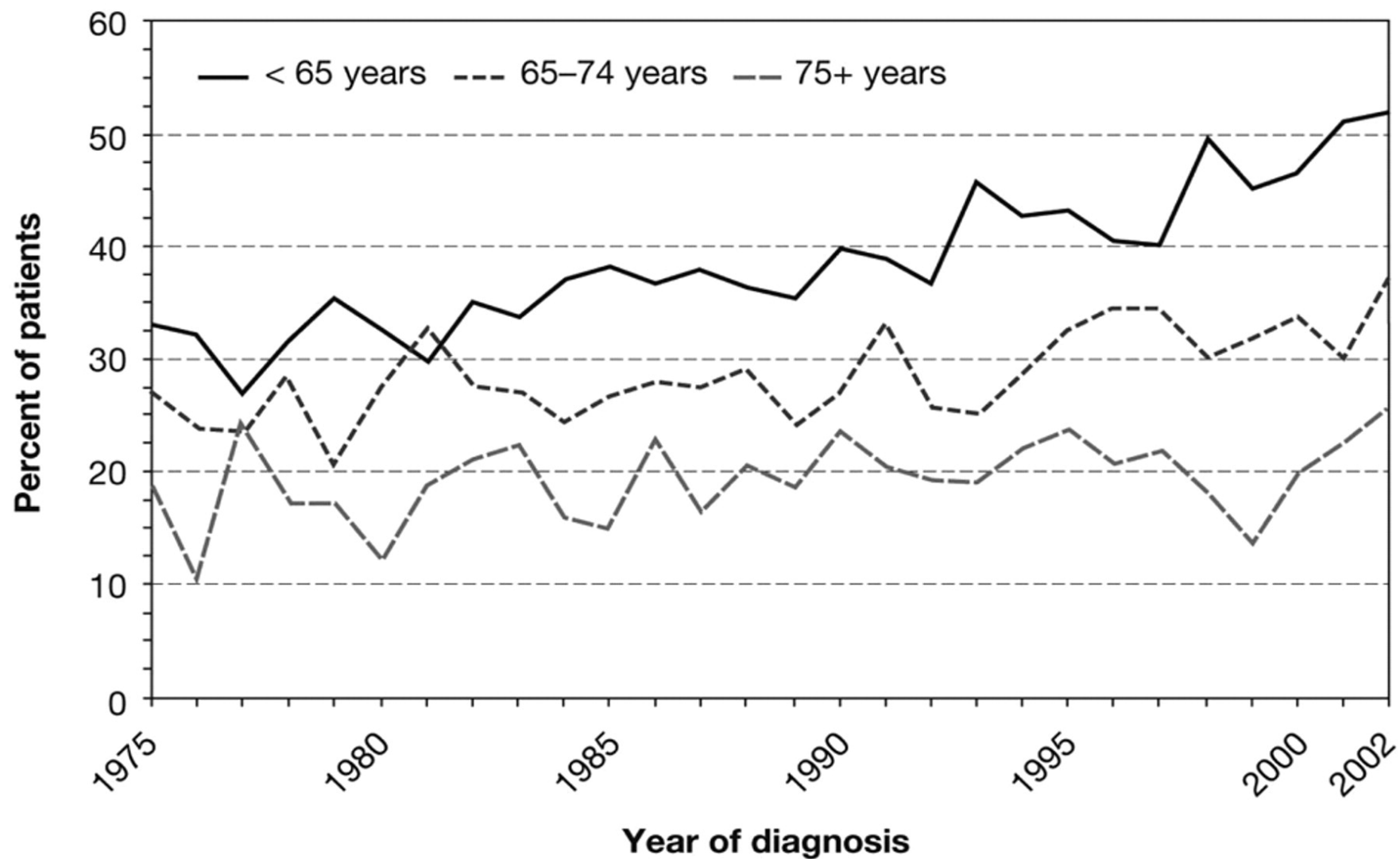


■ 0-49 anni ■ 50-69 anni ■ oltre 70 anni

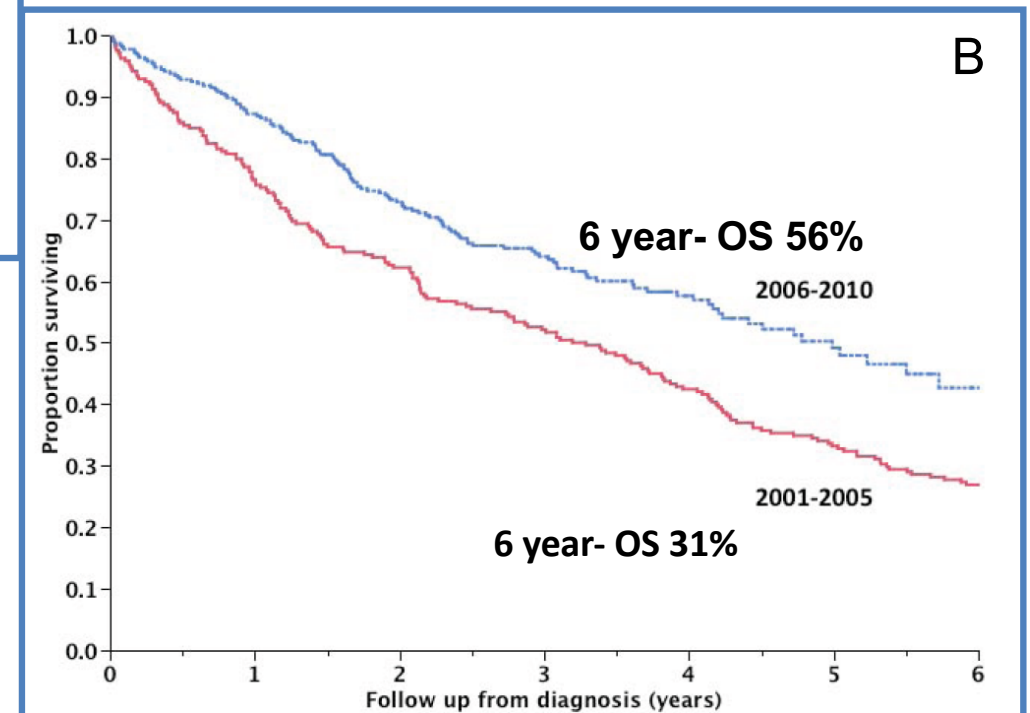
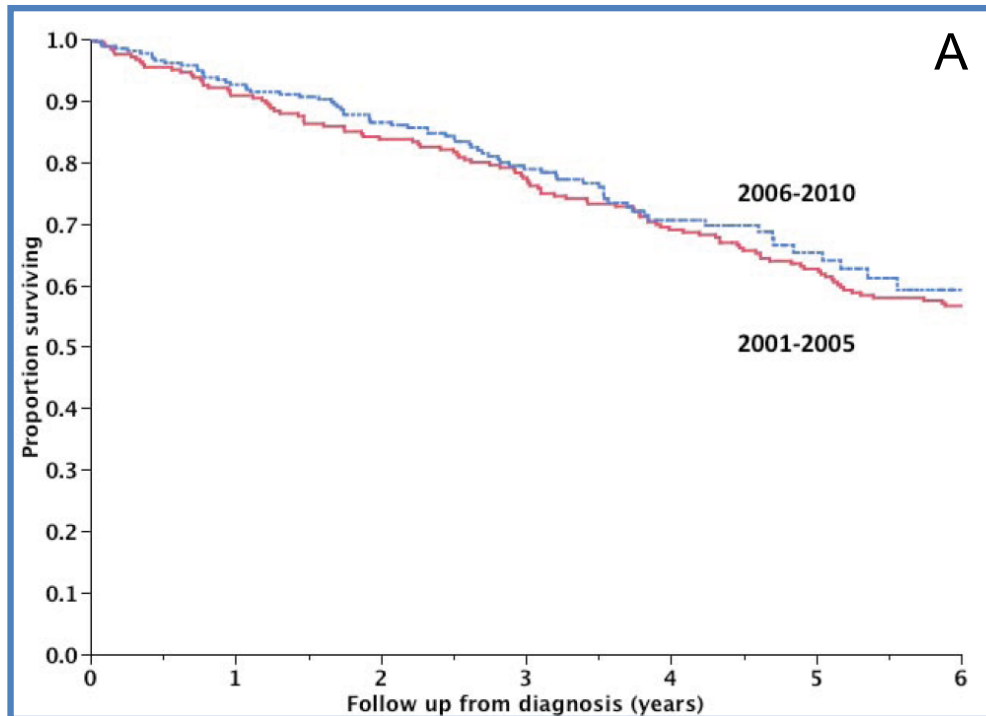
**433 casi nel 2015 in Veneto**

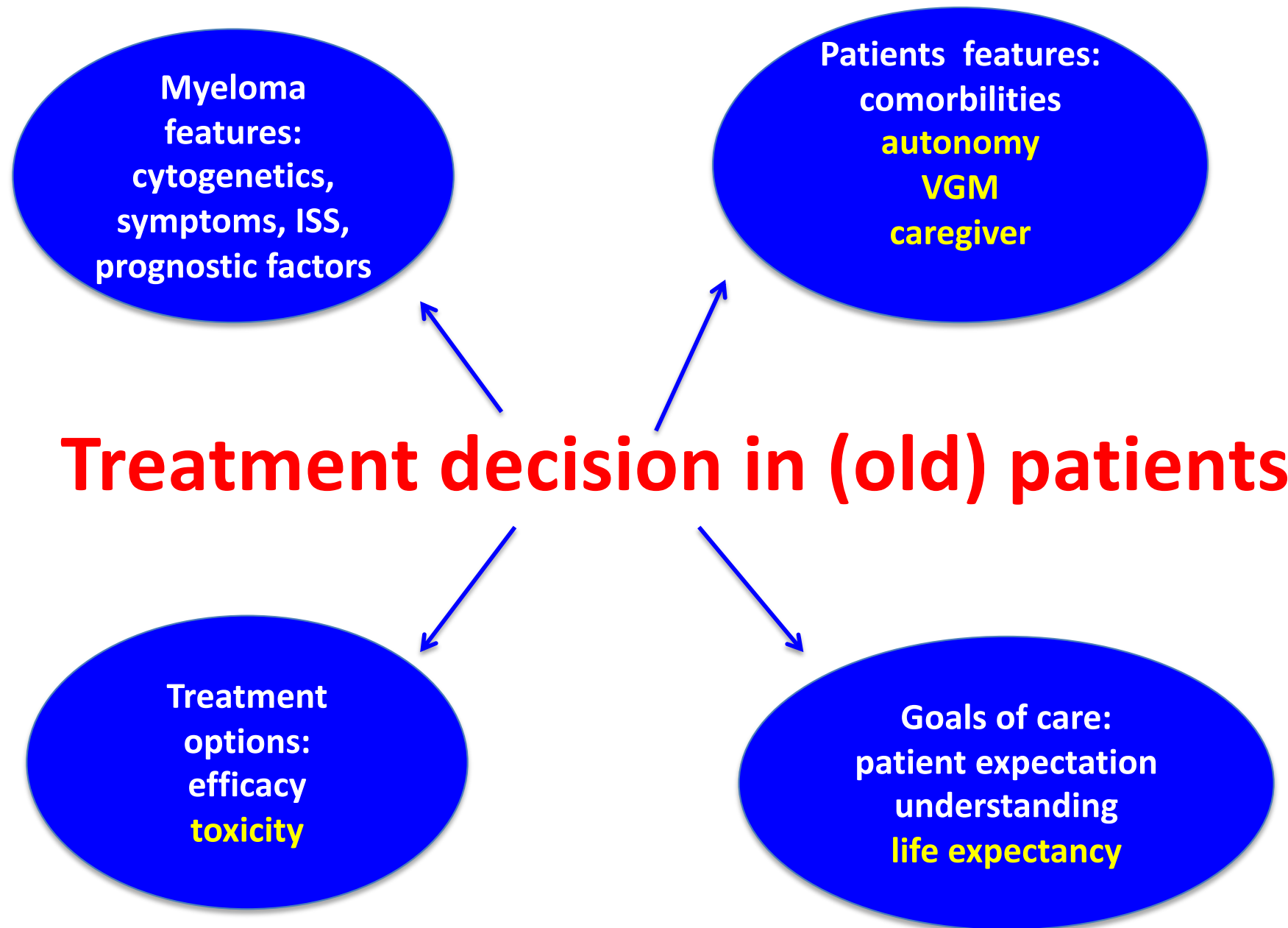
Nel  picco di incidenza nella fascia di età 80-85 anni (58 casi per 100.000 ab /anno)

## 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).**







# Chromosome Abnormalities

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

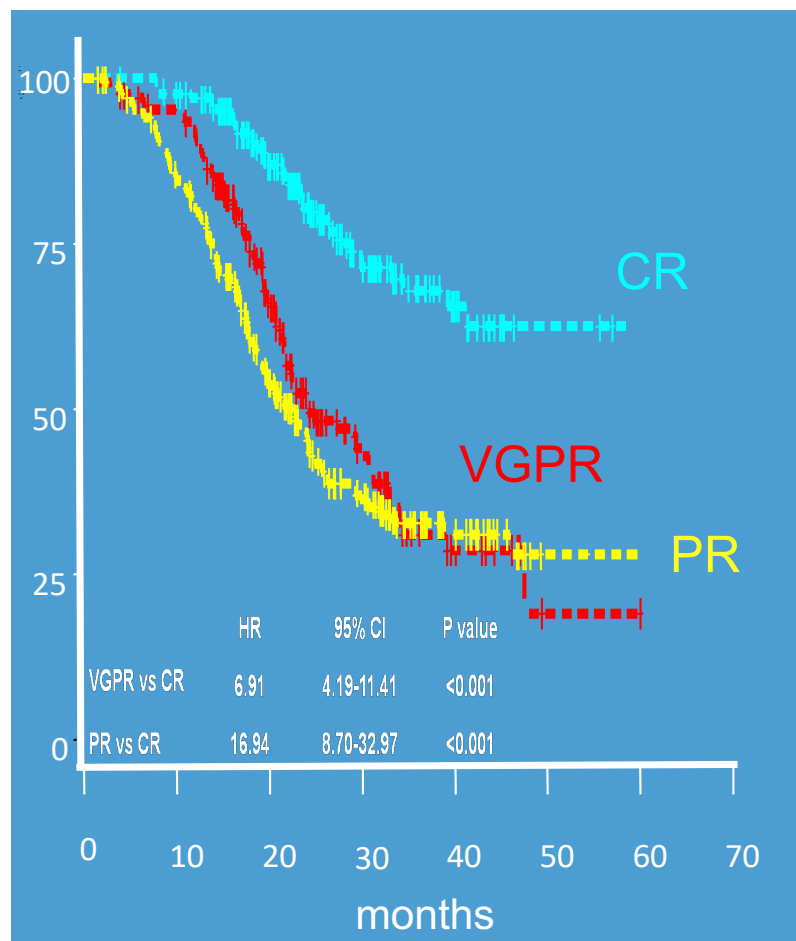
	Until 65 y n = 2347	66 – 75 y n = 1239	> 75 y n = 651	p value
Del 13	45%	43.6%	37%	0.004
t (4;14)	14.3%	10.9%	8.3%	<.0001
Del 17p	6%	5.9%	6.1%	NS

*Avet-Loiseau H. et al , 2011*

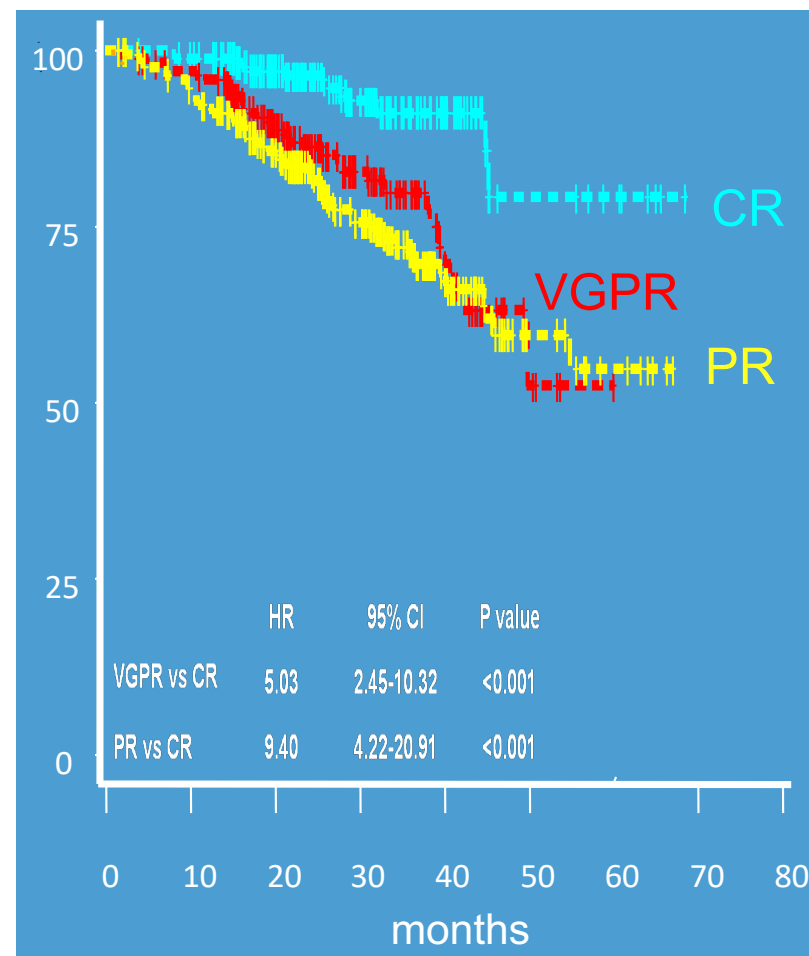
# CR predicts long term outcome

## Analysis of 1175 elderly patients

PFS

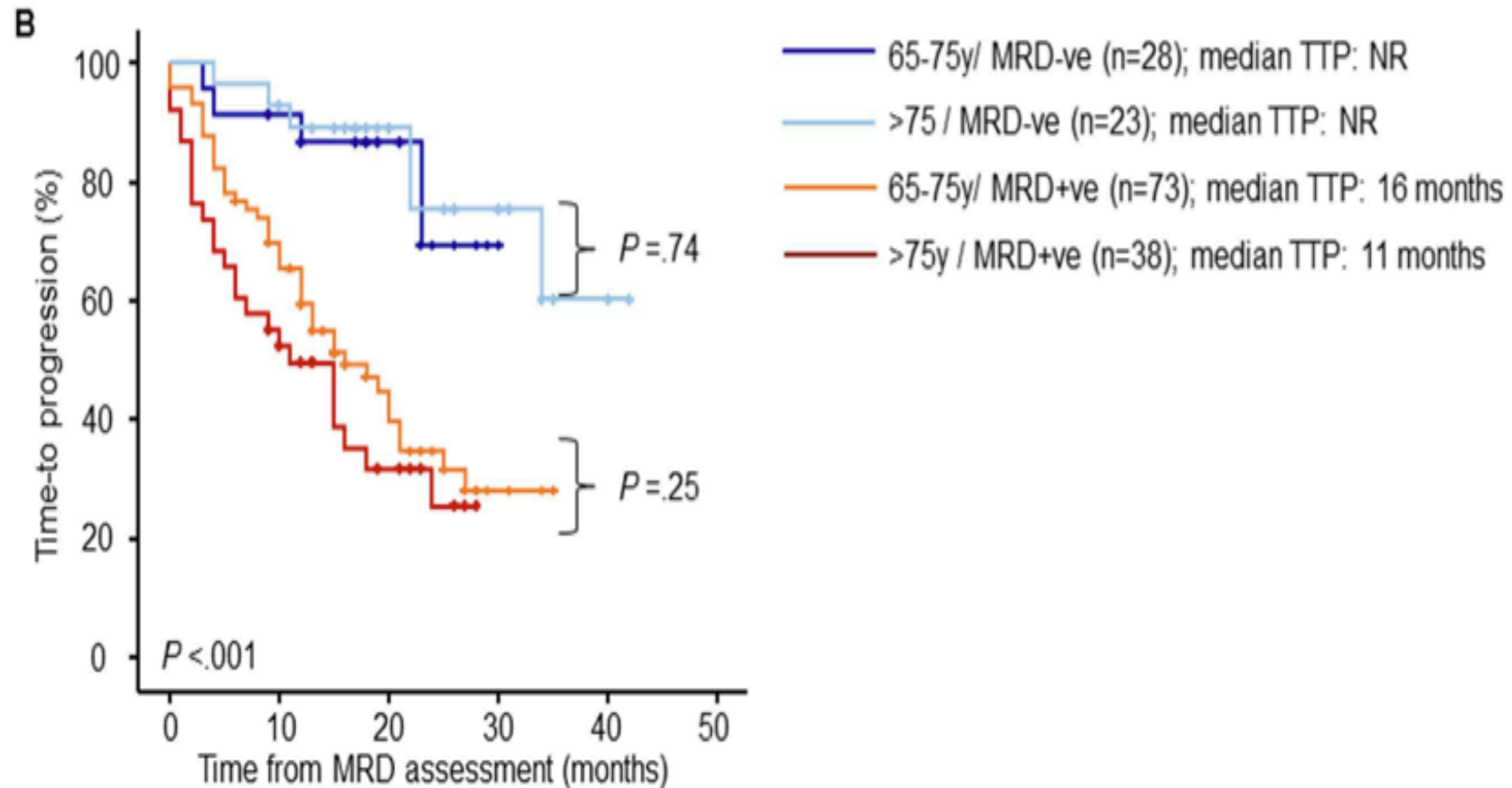


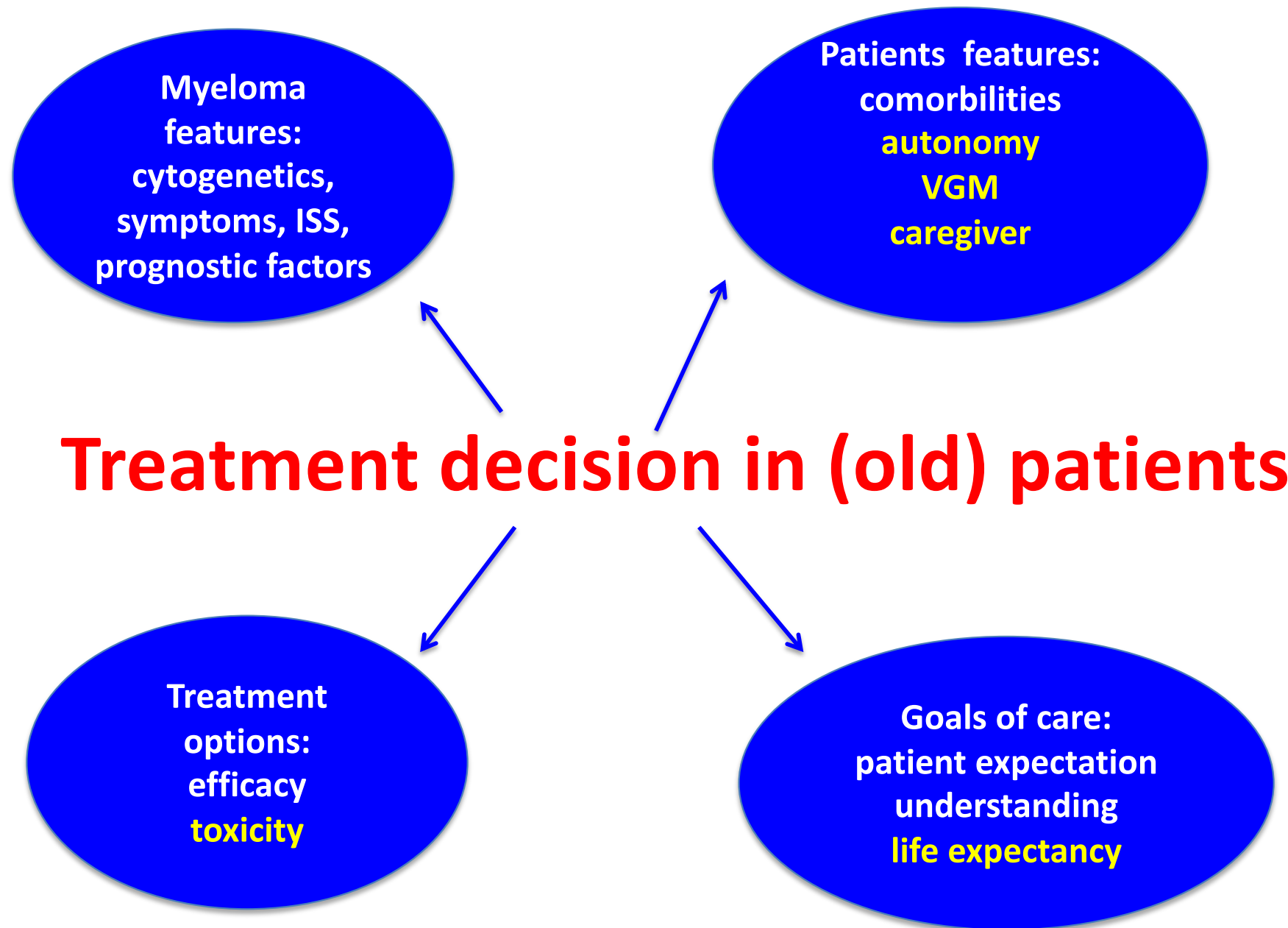
OS

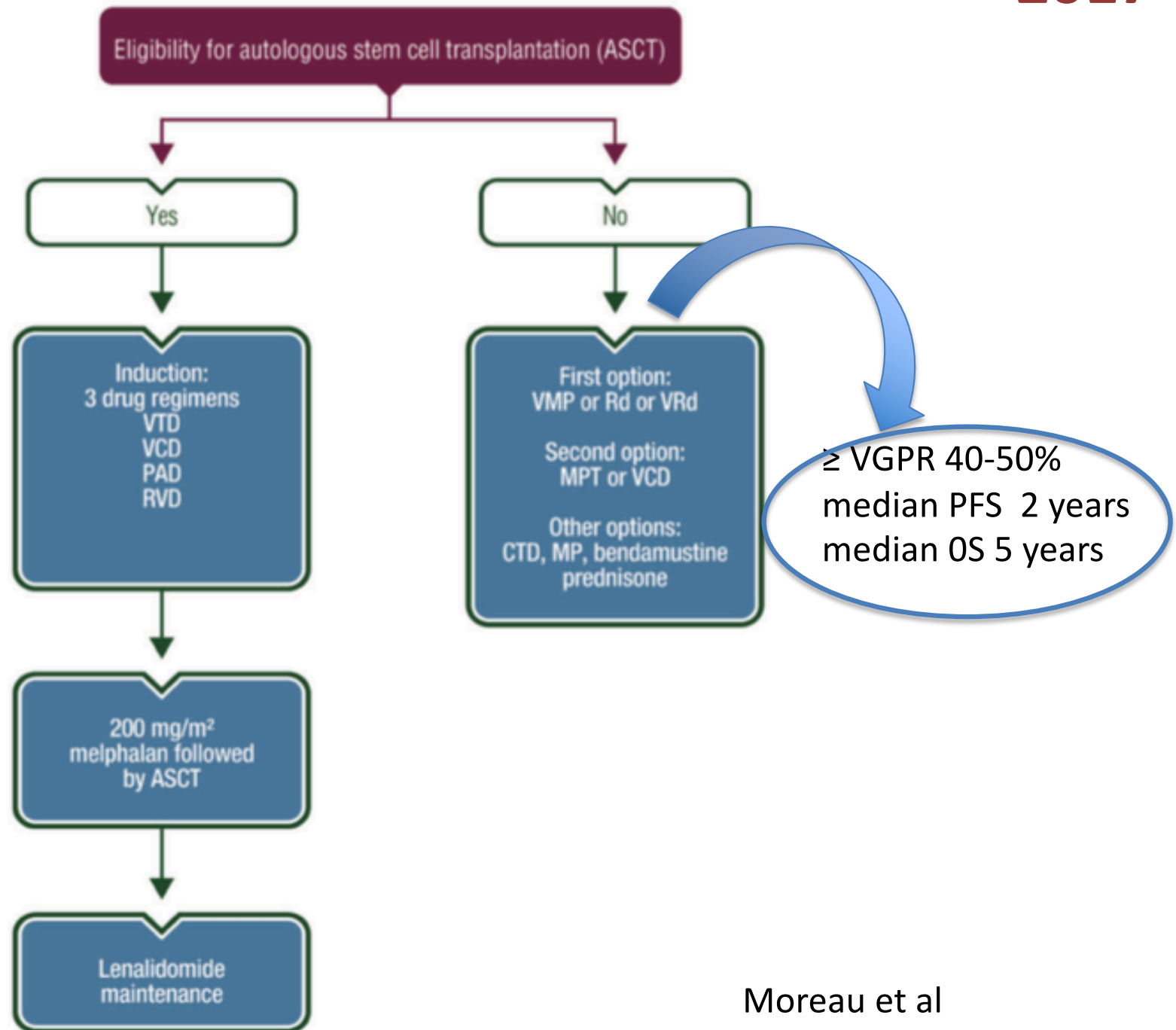




# Impact of reaching MRD negativity on time-to progression according to patients' age (n=162)





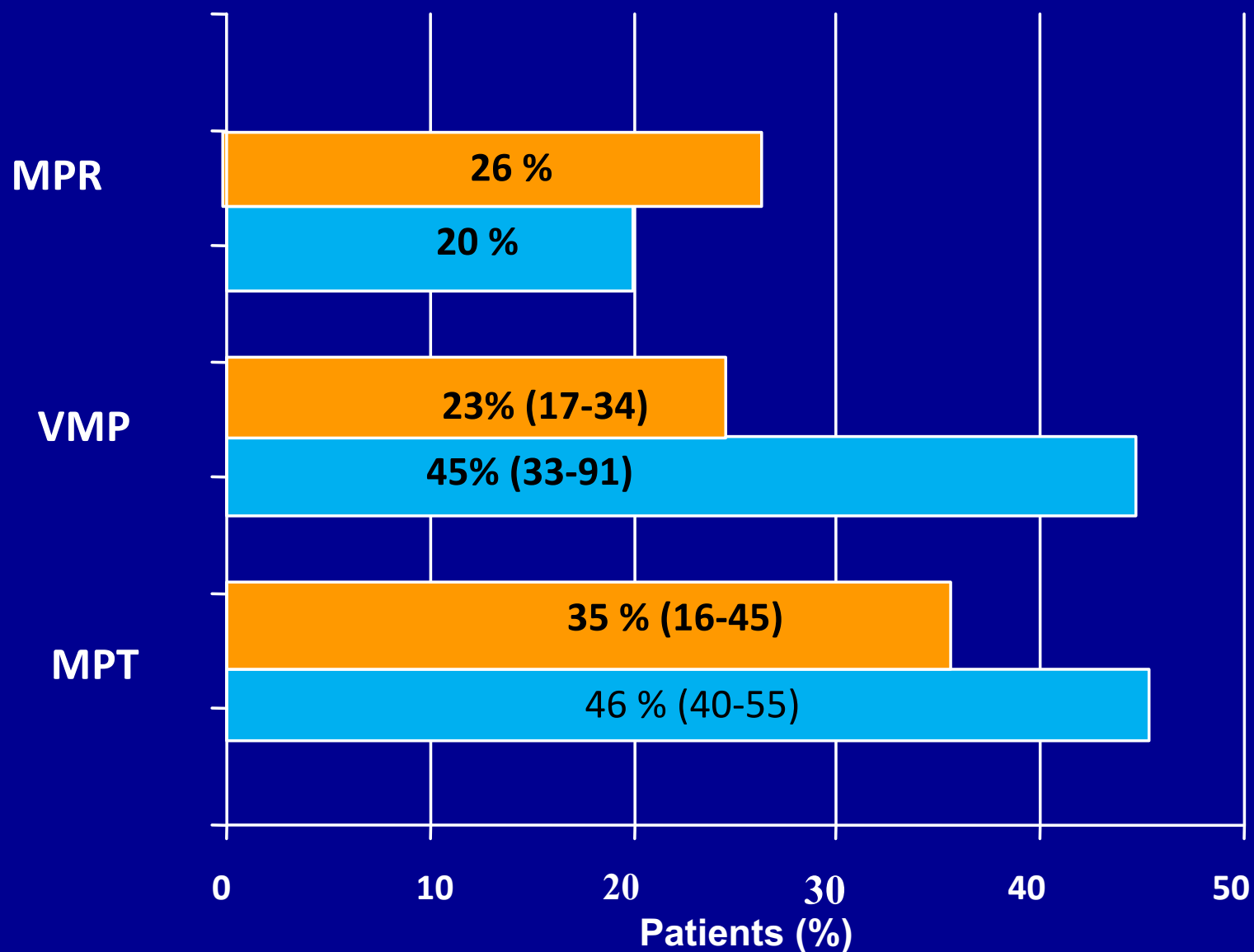




**non-haematol grade 3-5 AE**  
**Neuropathy, cardiac events,**  
**thrombosis, infections**



**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%
<b>Standard dose therapies</b>				
<b>VMP</b> <b>Bortezomib</b> <b>1,4,8,11</b>	<b>91</b>	<b>34</b>	<b>21.7 mo</b>	<b>46% at 5 y</b>
<b>RD</b> <b>Dexa 480 mg /mo</b>	<b>52</b>	<b>27</b>	<b>22.3</b>	<b>78% at 2 y</b>
<b>Lower dose therapies</b>				
<b>VMP</b> <b>Bortezomib</b> <b>1,8,15,21</b>	<b>51</b>	<b>12-17</b>	<b>24.8 mo</b>	<b>51 % at 5 y</b>
<b>Rd</b> <b>Dexa 160 mg/mo</b>	<b>35</b>	<b>19</b>	<b>26.1 mo</b>	<b>88% at 2 y</b>

*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 $\leq 4$ IADL score $\leq 5$ CCI score $\geq 2$
$\leq 75$	Plus at least 2 of the following: ADL score $\leq 4$ IADL score $\leq 5$ CCI score $\geq 2$

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

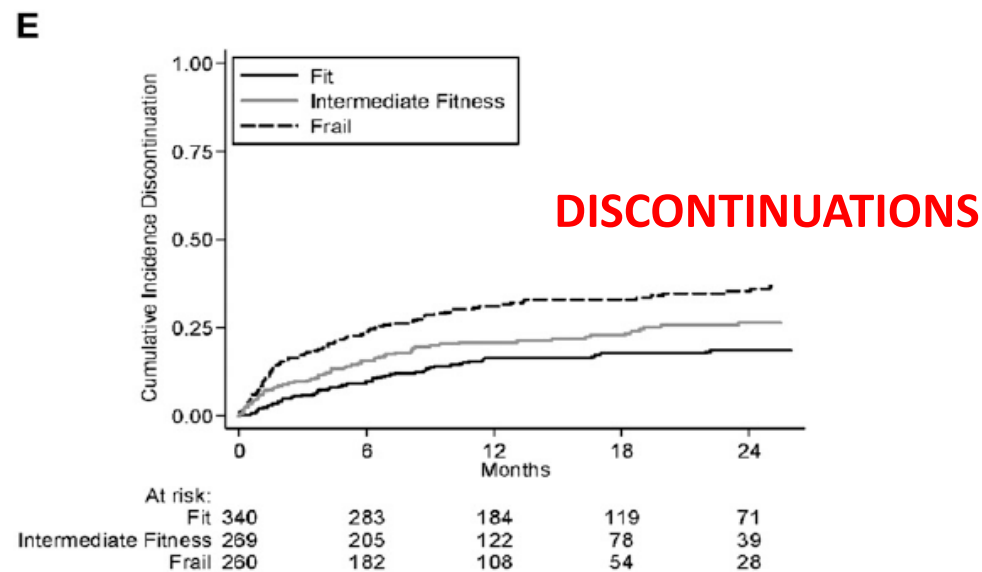
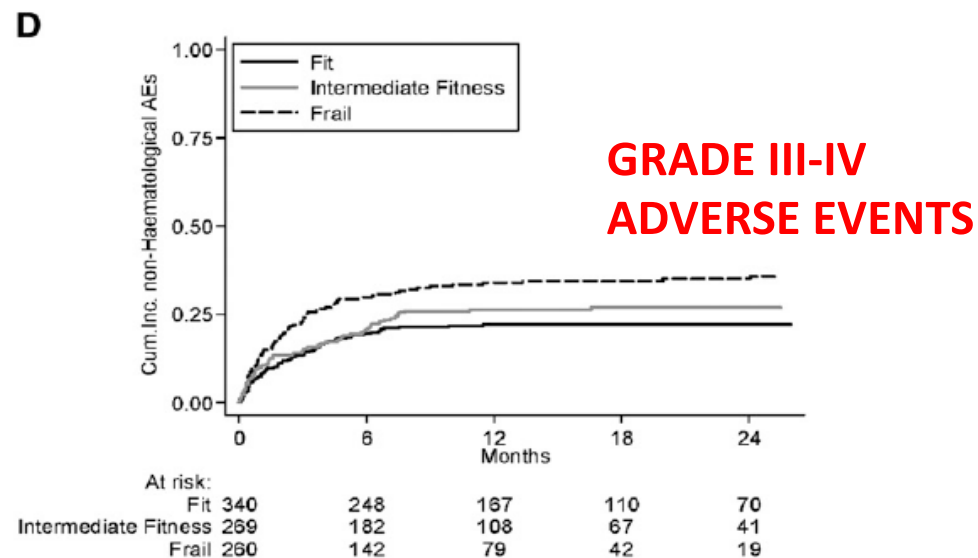
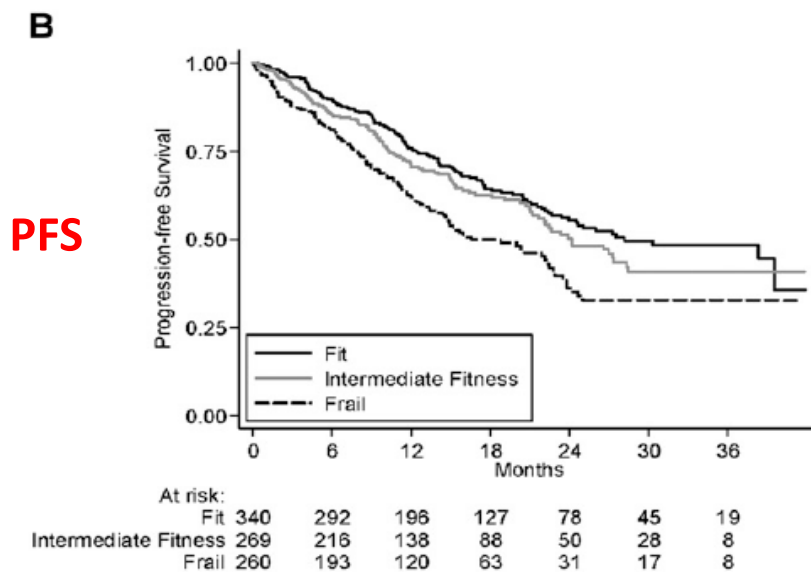
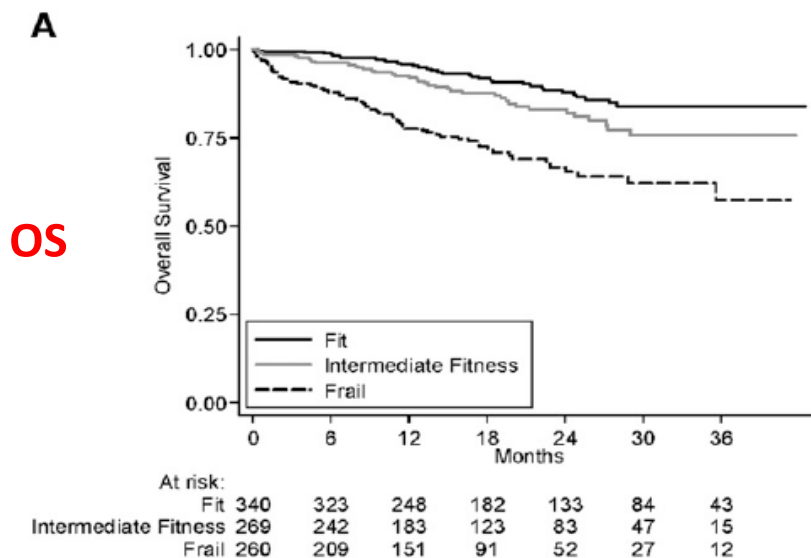
**How I treat fragile MM**  
**Larocca & Palumbo**  
**Blood Nov 2015**



# 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

## Rd<sup>1</sup>

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

## M<sup>2</sup>PR

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

## C<sup>3</sup>PR

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

2°  
R  
A  
N  
D  
O  
M  
I  
Z  
A  
T  
I  
O  
N

## MAINTENANCE

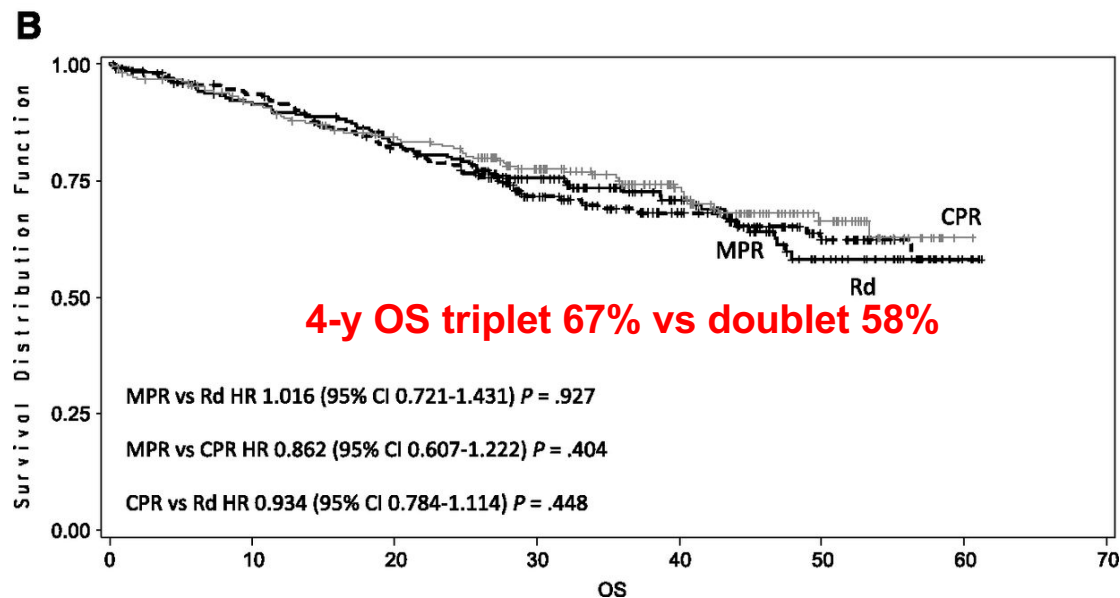
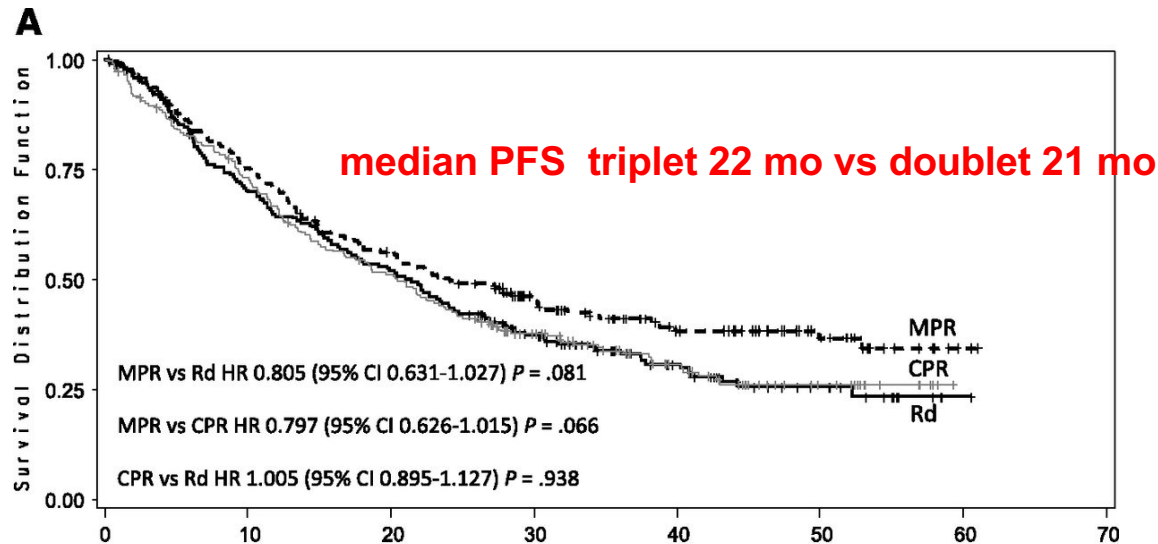
28-day courses until relapse  
R: 10 mg/day, days 1-21

## MAINTENANCE

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

75 years: <sup>1</sup>Dexamethasone 20 mg/week; <sup>2</sup>Melphalan 0.13 mg/Kg;  
<sup>3</sup>Cyclophosphamide: 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.

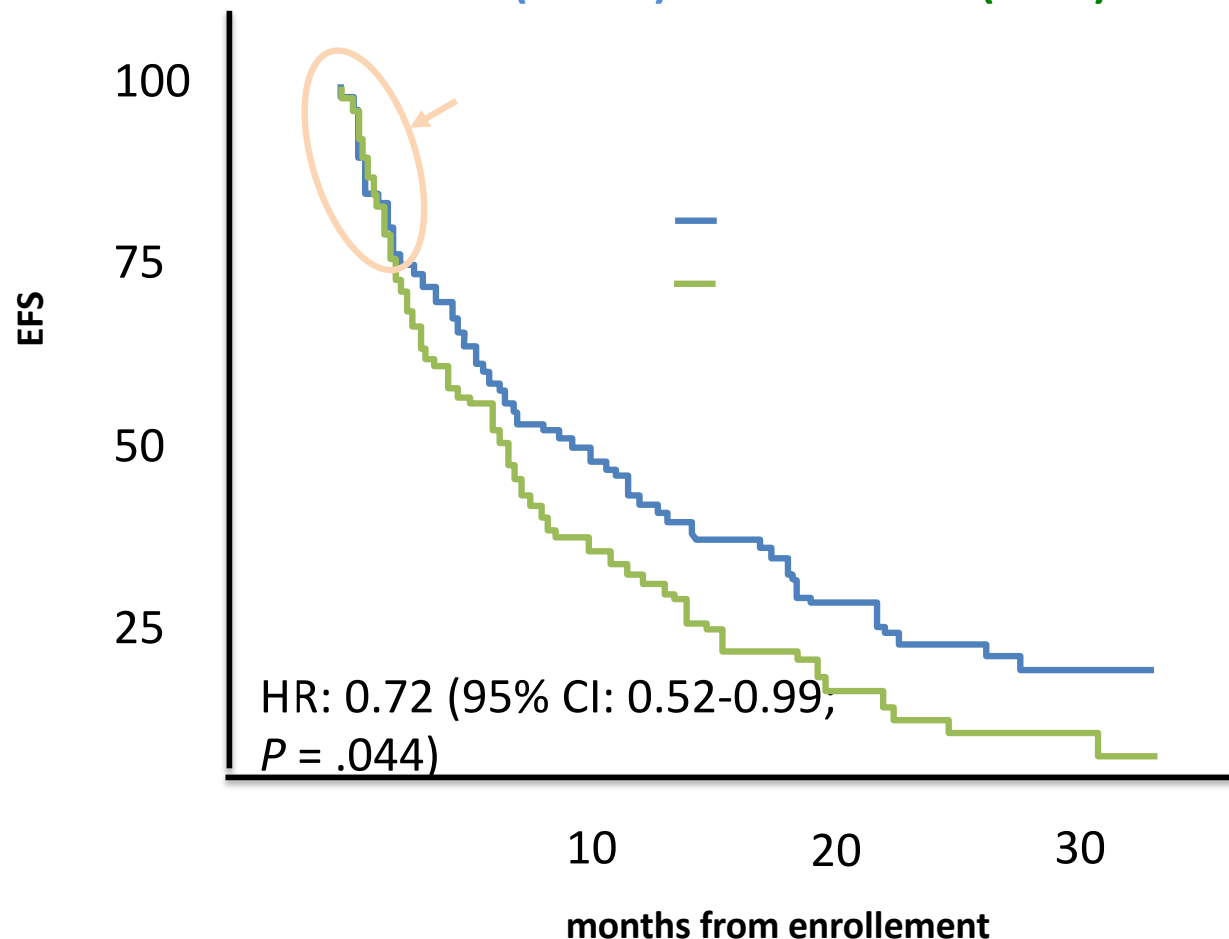
# Rd-R vs Continuous Rd in Intermediate-Fit Elderly Pts: Event-Free Survival (Primary Endpoint)

- 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 IMWG-frailty index points <i>CCI ≥ 2: 1</i> <i>IADL &lt; 5: 1</i> <i>ADL &lt; 4: 1</i> <i>Age 76–80: 1, &gt; 80: 2</i>	1 IMWG-frailty index point	2-5 IMWG-frailty index points

## REVISED MYELOMA COMORBIDITY INDEX (R-MCI): Age, KPS, renal function, lung function, frailty ± cytogenetics

FIT	INTERMEDIATE	FRAIL
0–3 R-MCI points <i>Age 60–69: 1, ≥ 70: 2</i> <i>KPS: 80-90%: 2, &lt; 70%: 3</i> <i>Renal disease: eGFR &lt; 60: 1</i> <i>Lung disease: moderate/severe: 1</i> <i>Frailty: moderate or severe: 1 ± cytogenetics: unfavorable: 1</i>	4-6 R-MCI points	7-9 R-MCI points

## MAYO FRAILITY INDEX: Age, ECOG PS, NT-proBNP

STAGE I	STAGE II/ STAGE III	STAGE IV
0 Mayo frailty index points  <i>Age ≥ 70: 1</i> <i>ECOG PS ≥ 2: 1</i> <i>NT-proBNP ≥ 300 ng/L: 1</i>	1 (STAGE II) Mayo frailty index point 2 (STAGE III) Mayo frailty index points	3 Mayo frailty index points

# 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**

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## GOAL OF TREATMENT

### FIT

Efficacy: deep response

### INTERMEDIATE

Balance efficacy and toxicity

### FRAIL

Conservative approach, low toxicity

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## 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

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# NCCN Guidelines Version 1.2020

## Multiple Myeloma

### MYELOMA THERAPY<sup>a-c,e-g,i,j</sup>

#### PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES

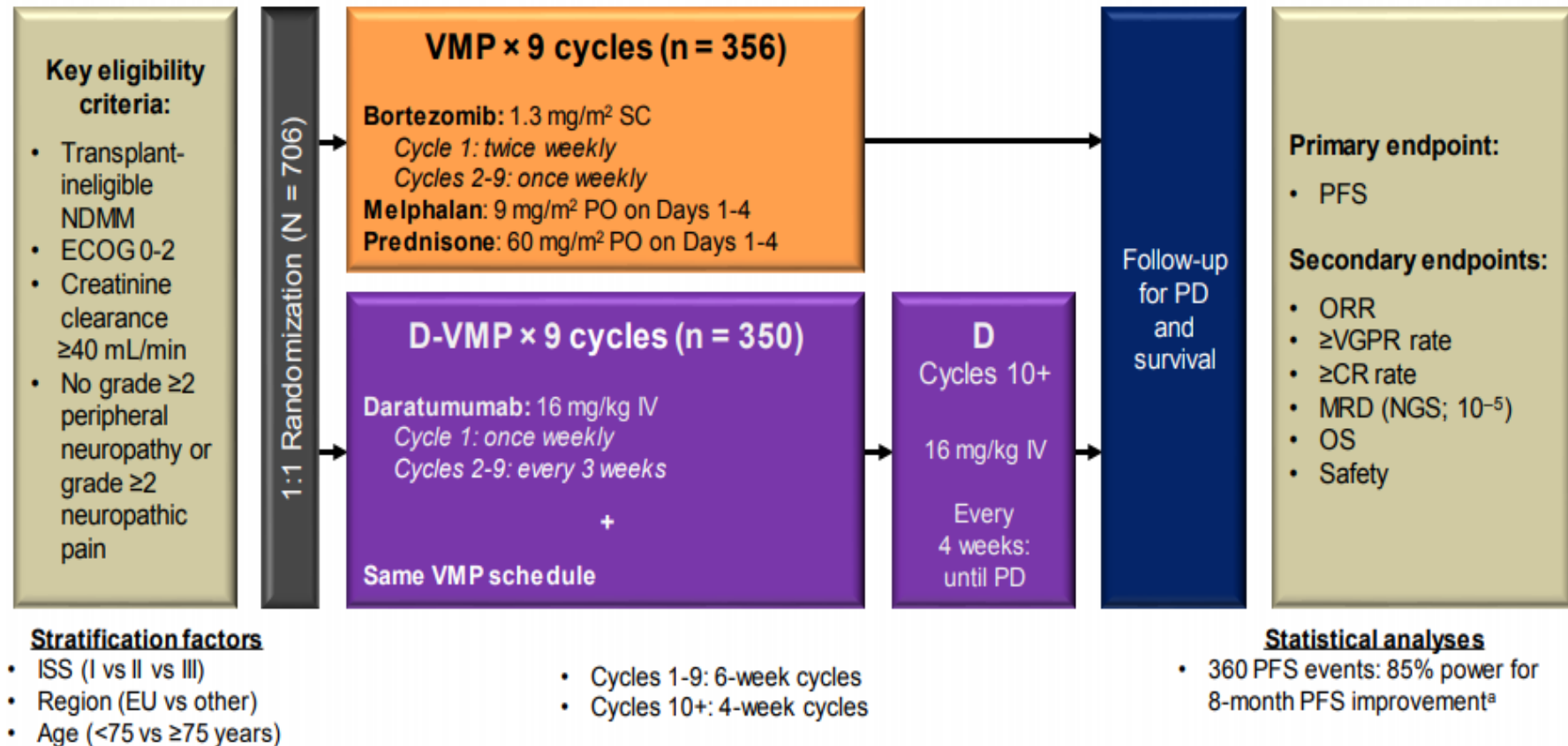
##### Preferred Regimens

- Bortezomib/lenalidomide/dexamethasone (category 1)<sup>o</sup>
- Daratumumab<sup>p</sup>/lenalidomide/dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)<sup>k,q</sup>
- Bortezomib/cyclophosphamide/dexamethasone<sup>n</sup>

##### Other Recommended Regimens

- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone
- Daratumumab<sup>p</sup>/bortezomib/melphalan/prednisone (category 1)

# Alcyone: study design



356 patients  
 $\geq 75$  y: 30%  
 ECOG 0-1: 80%  
 Standard risk cyto: 84%

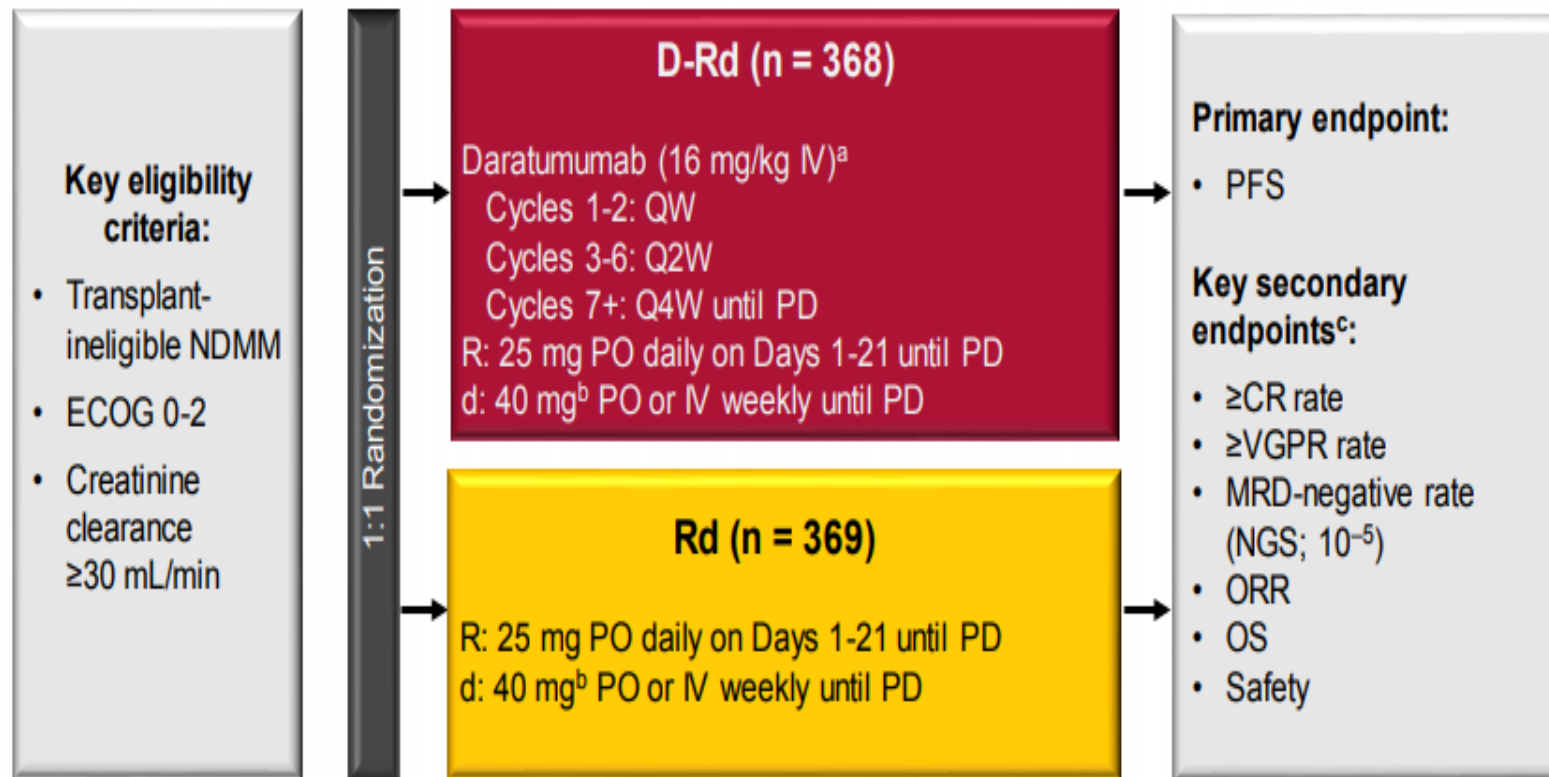
Mateos et al. N E J M 2018

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  $\geq 75$  years)

Cycle: 28 days

<sup>a</sup>On 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.

<sup>b</sup>For patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.

<sup>c</sup>Efficacy endpoints were sequentially tested in the order shown.

737 patients

$\geq 75$  y: 44%

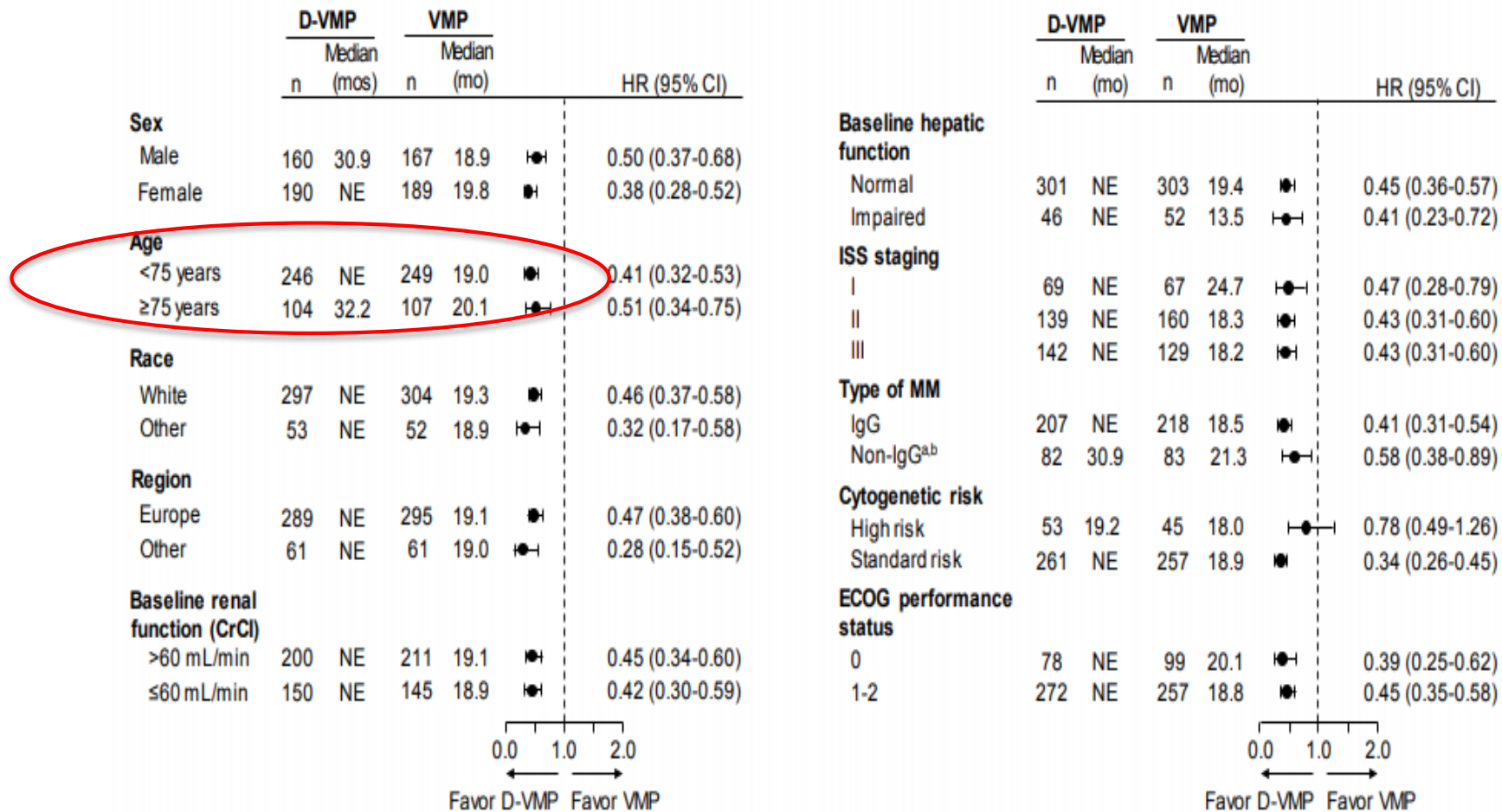
ECOG 0-1: 84%

Standard risk cyto :86%

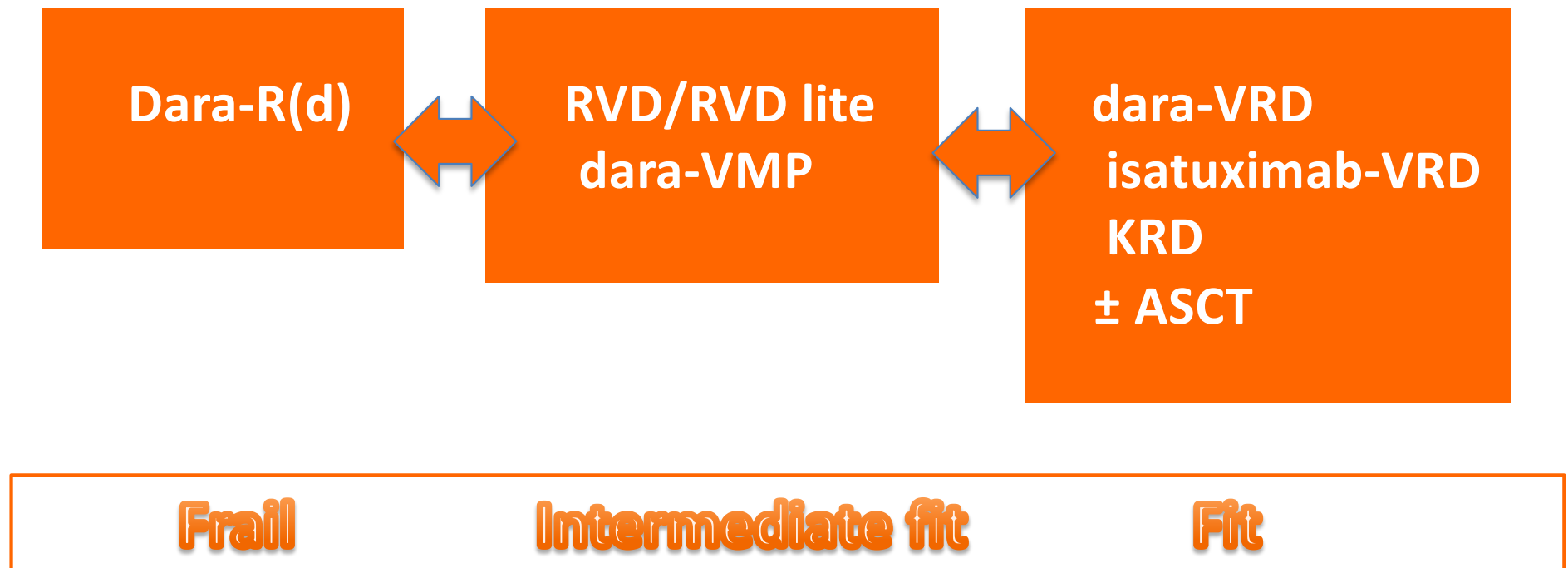
# OUTCOME OF NEW STANDARDS

	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
Extrahemat toxicity	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°  
R  
A  
N  
D  
O  
M  
I  
Z  
A  
T  
I  
O  
N

## 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

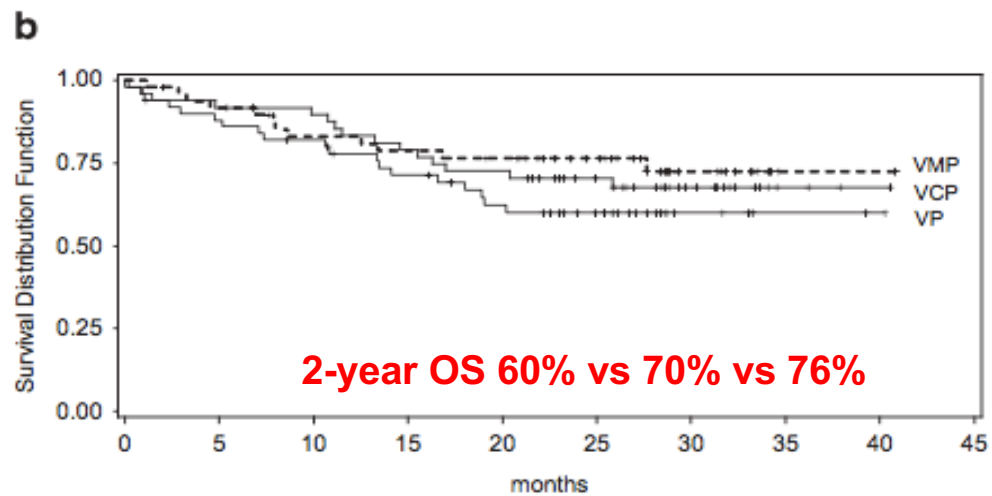
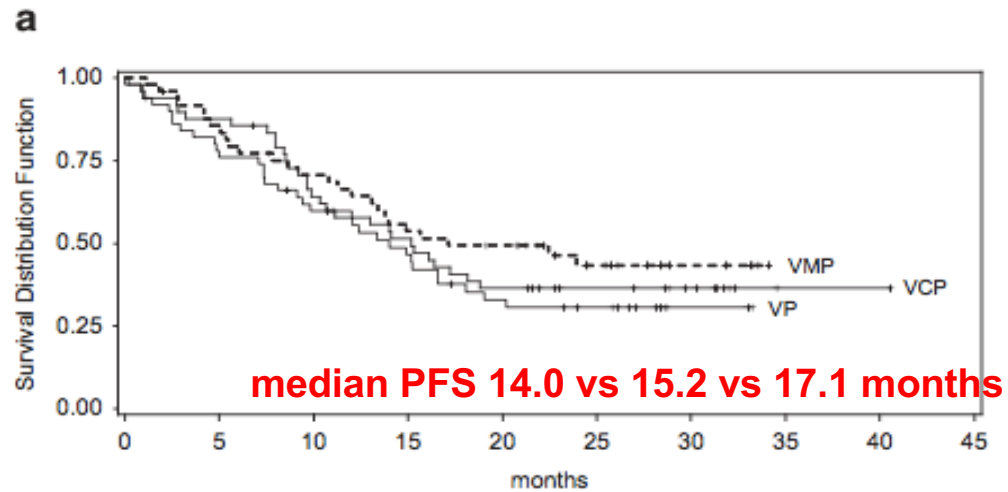
P: 50 mg, every other day

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

**FIT**

**INTERMEDIATE**

**FRAIL**

organ disfunction  
**Life expectancy**

Co-morbidities,

**Impaired functional status**



**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

```
graph TD; Title[Treatment Decision in Older Patients] -- Green Arrow --> Patients[Patients<br/>• ADL<br/>• IADL<br/>• Comorbidities<br/>• Hospitalization<br/>• Medications<br/>• Social Support]; Title -- Red Arrow --> MM[Multiple Myeloma<br/>• Cytogenetics<br/>• Stage<br/>• Tumor burden<br/>• Optimal Chemo<br/>• Supportive meds]; Title -- White Arrow --> Goals[Goals of Care (CR vs Disease Control?)<br/>Expectations<br/>Understanding<br/>Life Expectancy];
```

## 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

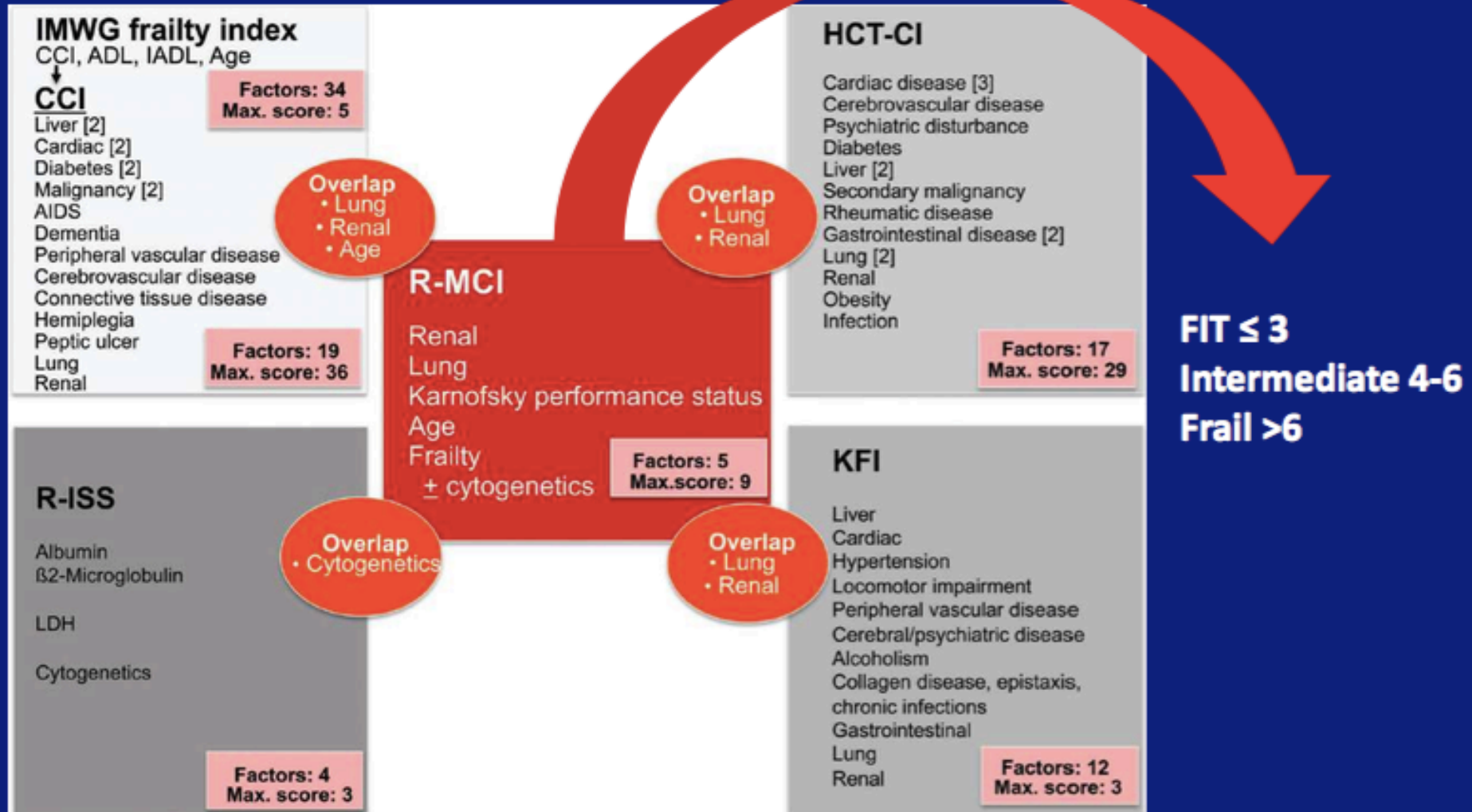
agent	FIT patients Level 0	UNFIT patients Level -1	FRAIL patients Level -2
thalidomide	100 mg/d	50 mg/d	50 mg/qod
Lemalidomide	25 mg/d 1-21	15 mg/d 1-21	10 mg/d 1-21
Bortezomib	1,3 mg/mq 1,4,8,11	1,3 mg/mq 1,8,15,21	1,0 mg/mq 1,8,15,21
Dexamethasone	160 mg/4w	80 mg/4w	40 mg/4w
prednisone	60 mg/mq 1-4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

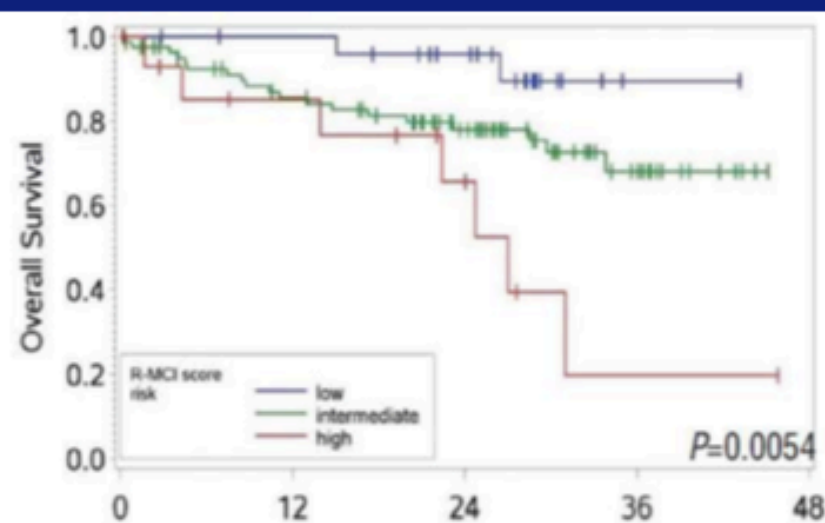
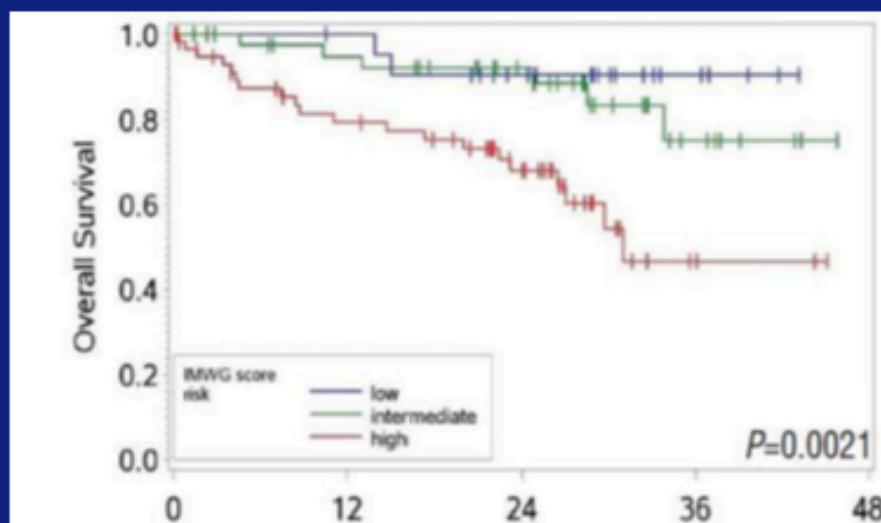
Variables	Mild Moderate	Definition and grading	Severe
1. Renal function: eGFR / serum creatinine	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4
2. Lung function: dyspnea or FEV <sub>1</sub> /FVC, FEV <sub>1</sub> , TLC, respiratory insufficiency	dyspnea upon intense activity, mildly altered lung function	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 <sub>1</sub> <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	i.v. 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



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

Monika Engelhardt,<sup>1</sup> Sandra Maria Dold,<sup>1</sup> Gabriele Ihorst,<sup>2</sup> Alexander Zober,<sup>1</sup> Mandy Möller,<sup>1</sup> Heike Reinhardt,<sup>1</sup> Stefanie Hieke,<sup>3</sup> Martin Schumacher,<sup>3</sup> and Ralph Wäsch<sup>1</sup>



<http://www.myelomacomorbidityindex.org>