

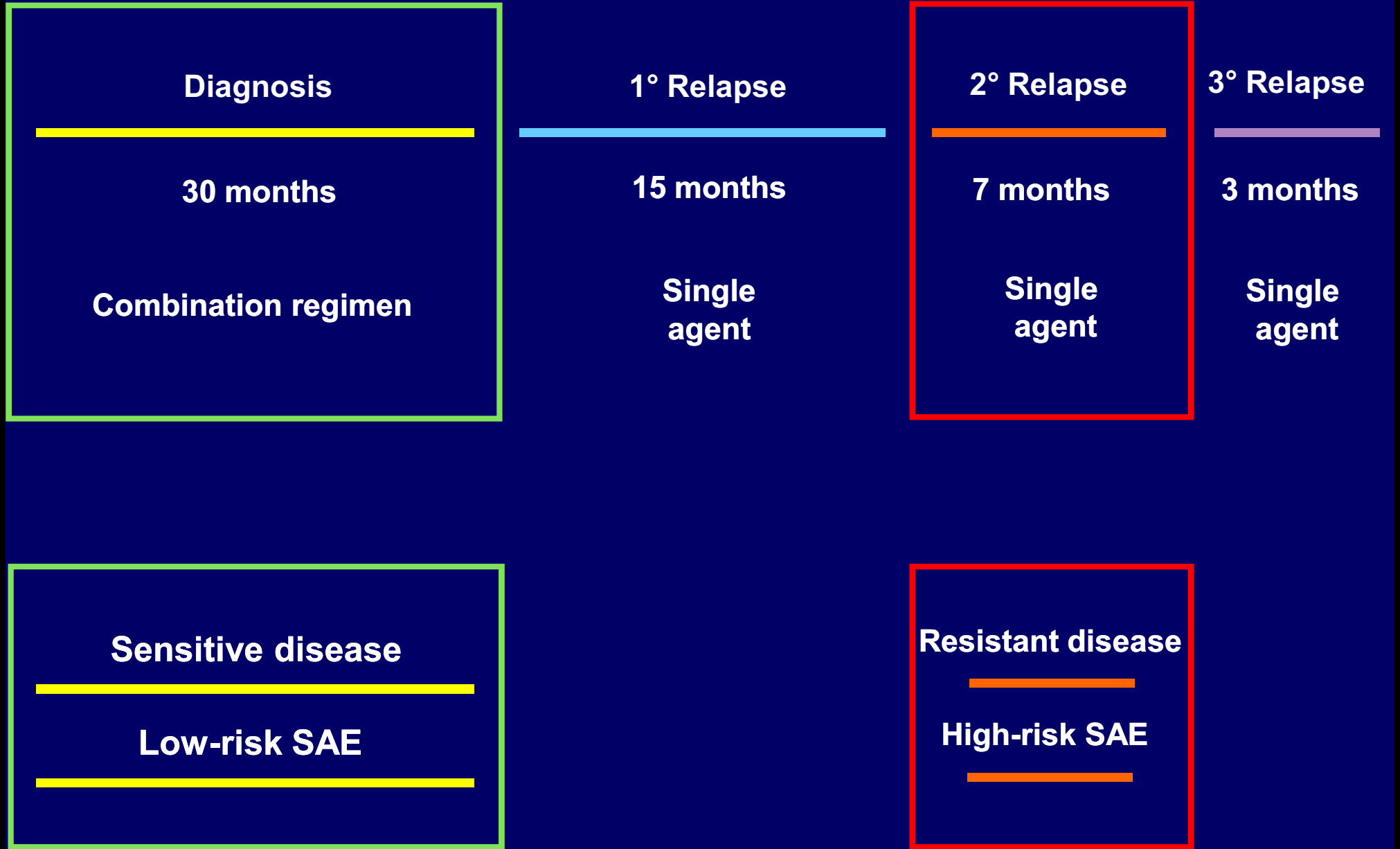
**Emerging Therapies
for
Transplantation-Ineligible
Patients With Myeloma**

Antonio Palumbo, MD

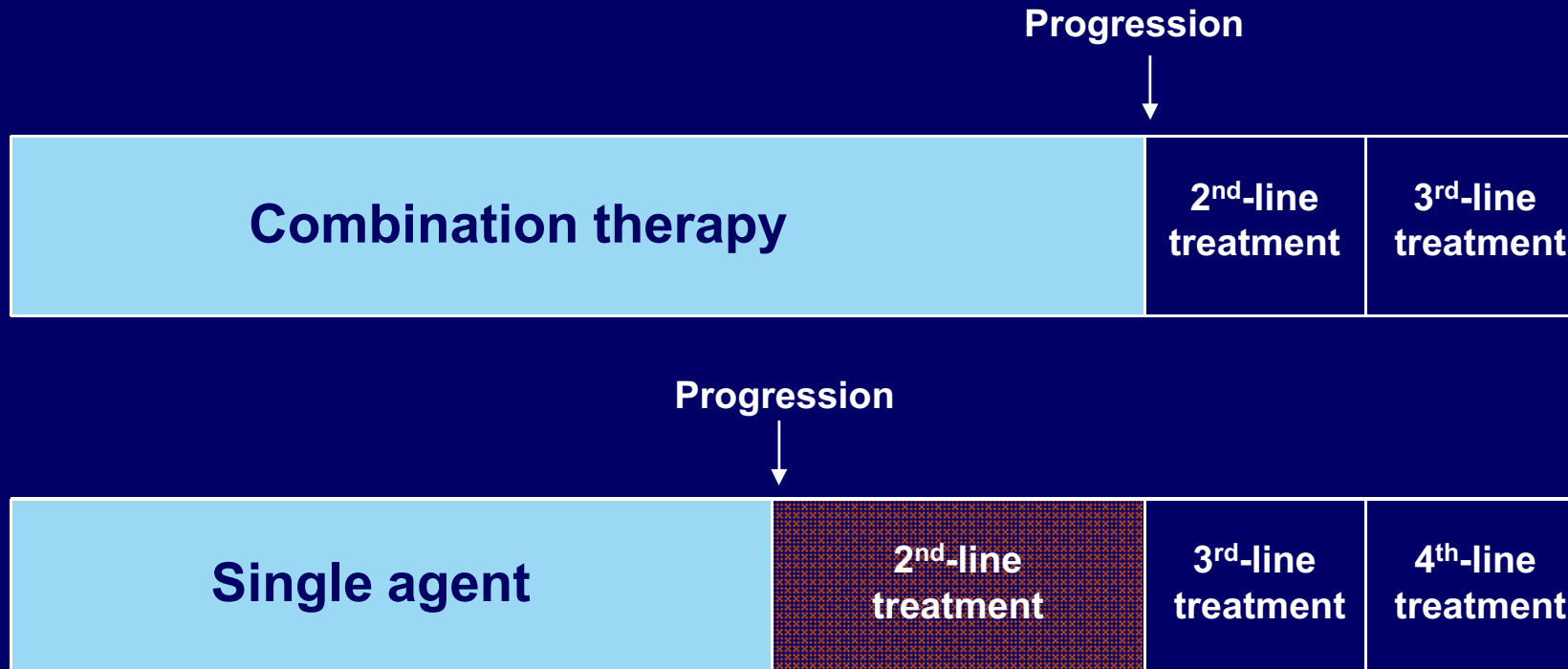
University of Torino, Torino, I, EU

Treatment strategies

Sensitive vs Resistant Disease



Combination Therapy vs Single Agent



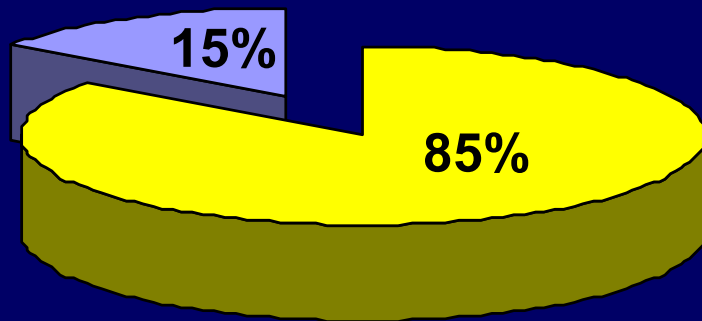
- **Combination could improve PFS only**
 - quality of life
- **Combination could improve OS**
 - evidence needed

Clinical Impact of VTD Consolidation in VGPR Patients After ASCT

Responses after ASCT

VGPR 85%

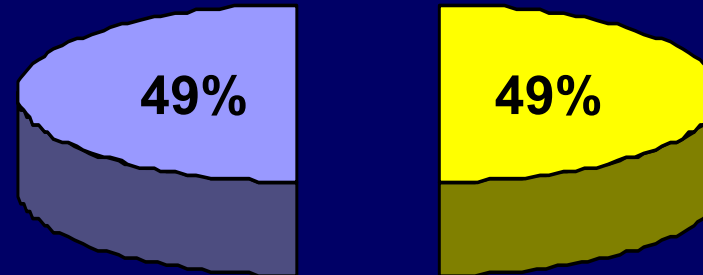
CR 15%



Responses after VTD

VGPR 49%

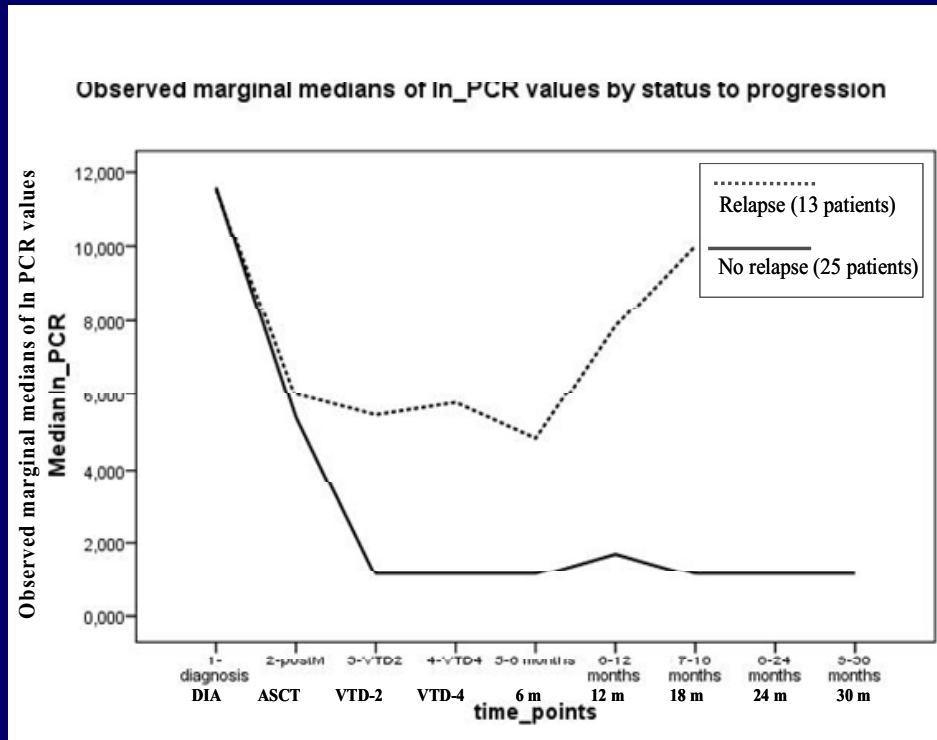
CR 49%



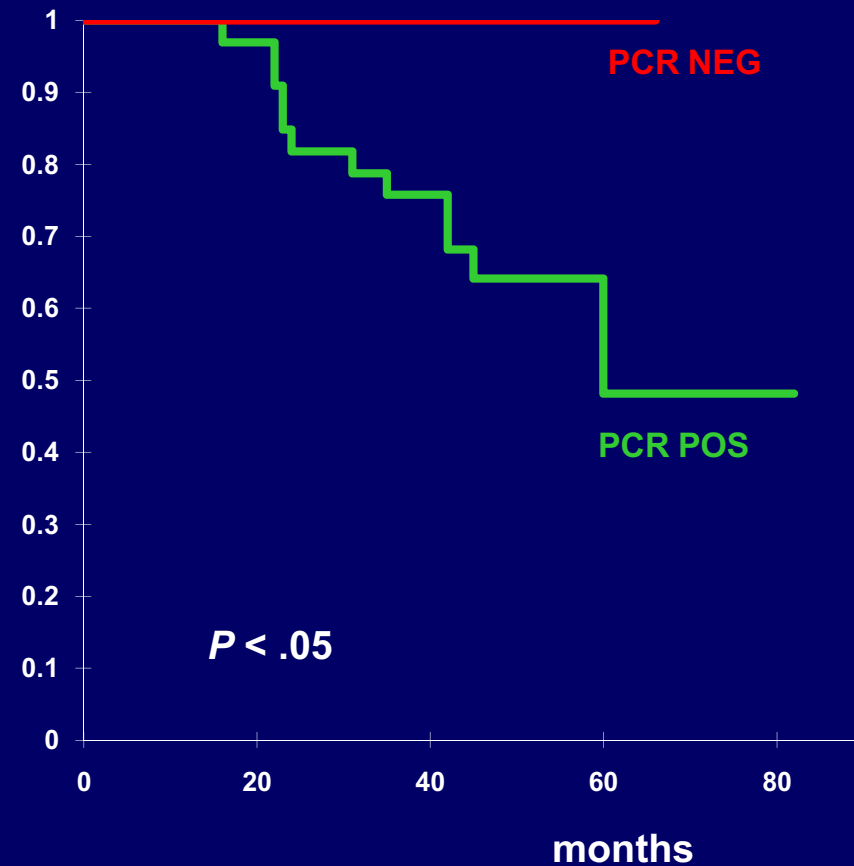
■ VGPR

■ CR

Clinical Impact of Minimal Residual Disease



PFS in PCR-negative patients



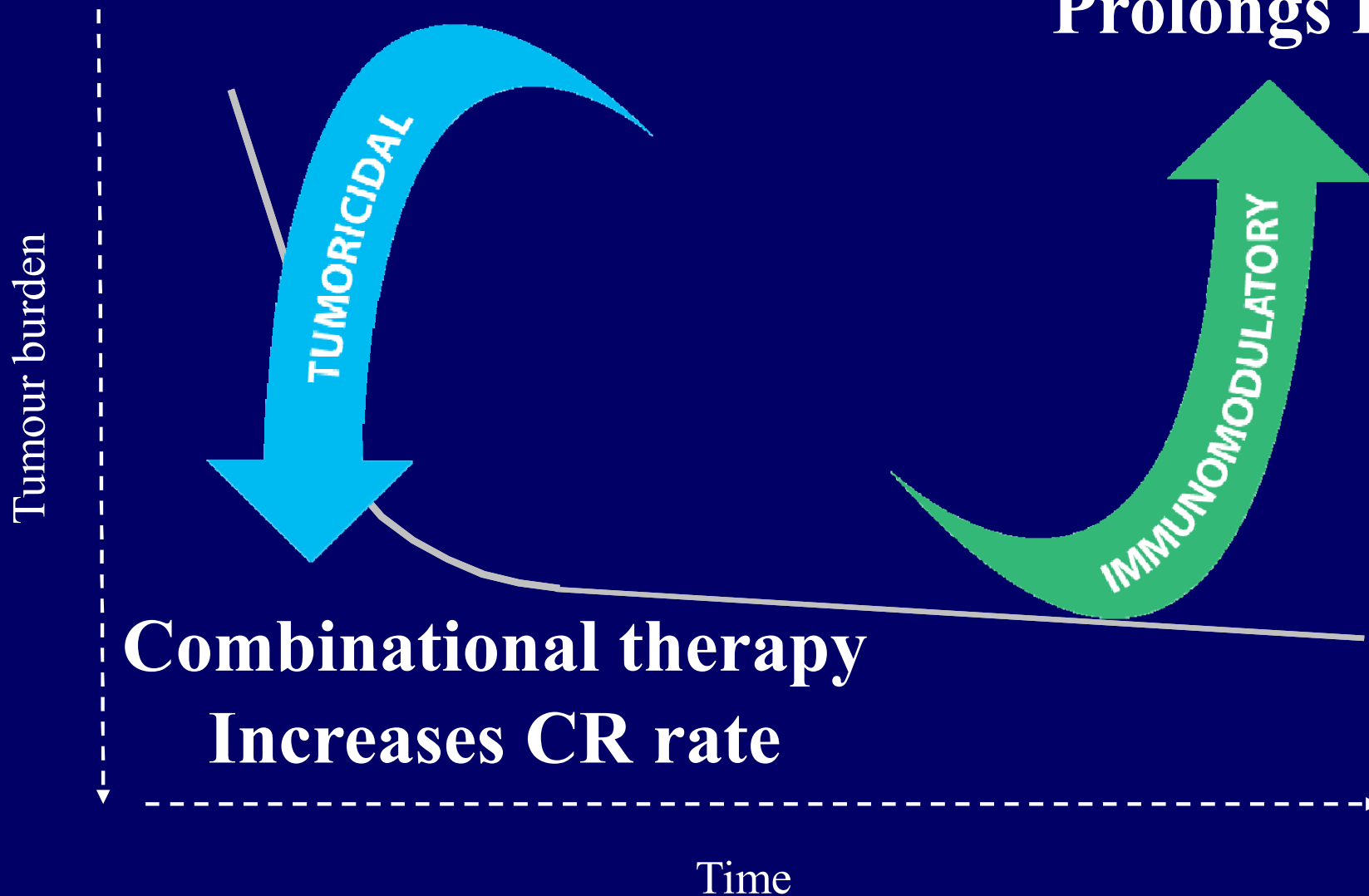
Complete Response are all the same?

Response Criteria	Tumor gene copy number
Diagnosis	25,000 - 500,000
PR	5,000 – 100,000
VGPR	1,500 – 20,000
Immunofixation-negative CR	1,000 – 10,000
Immunophenotypic CR*	10 – 100
Molecular CR^	5 – 20

*Paiva et al Blood 2009: 114;4369-72; ^Ladetto et al. J Clin Oncol . 2010;28(12):2077-84

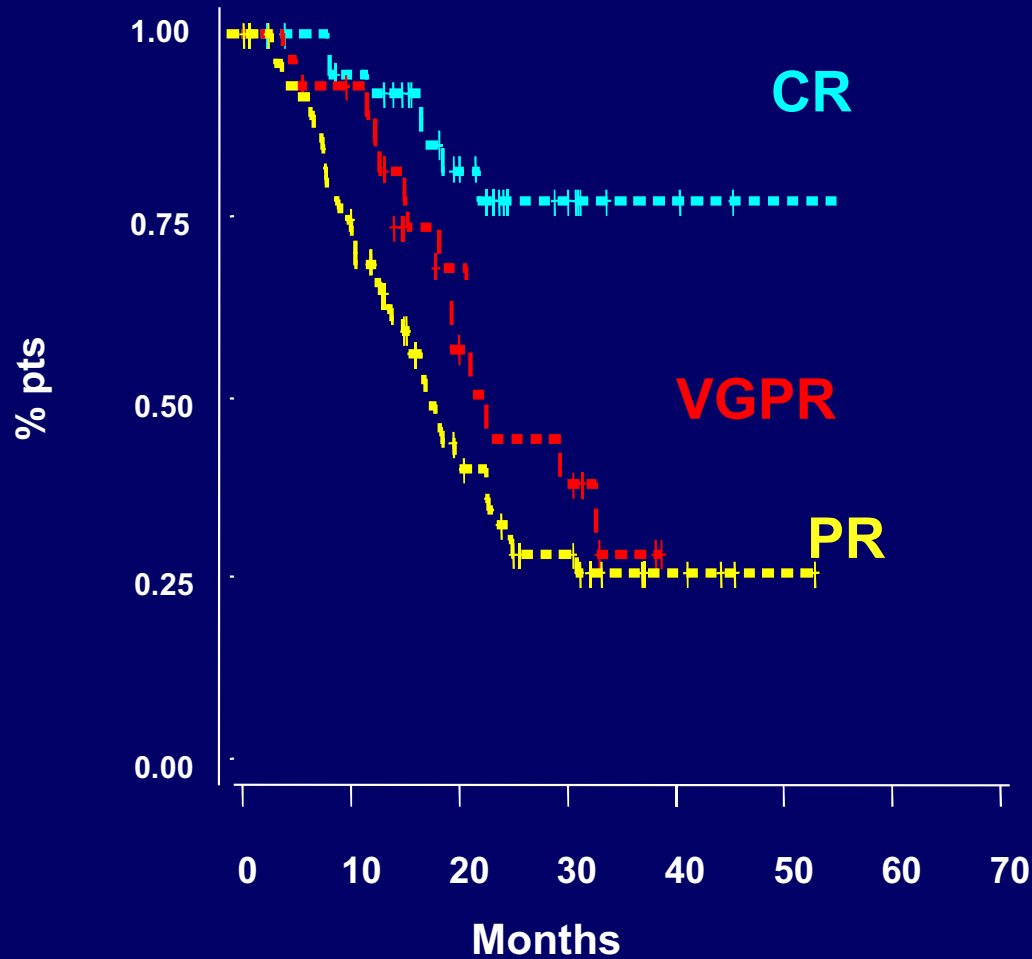
Treatment strategy

Continuous therapy
Prolongs PFS

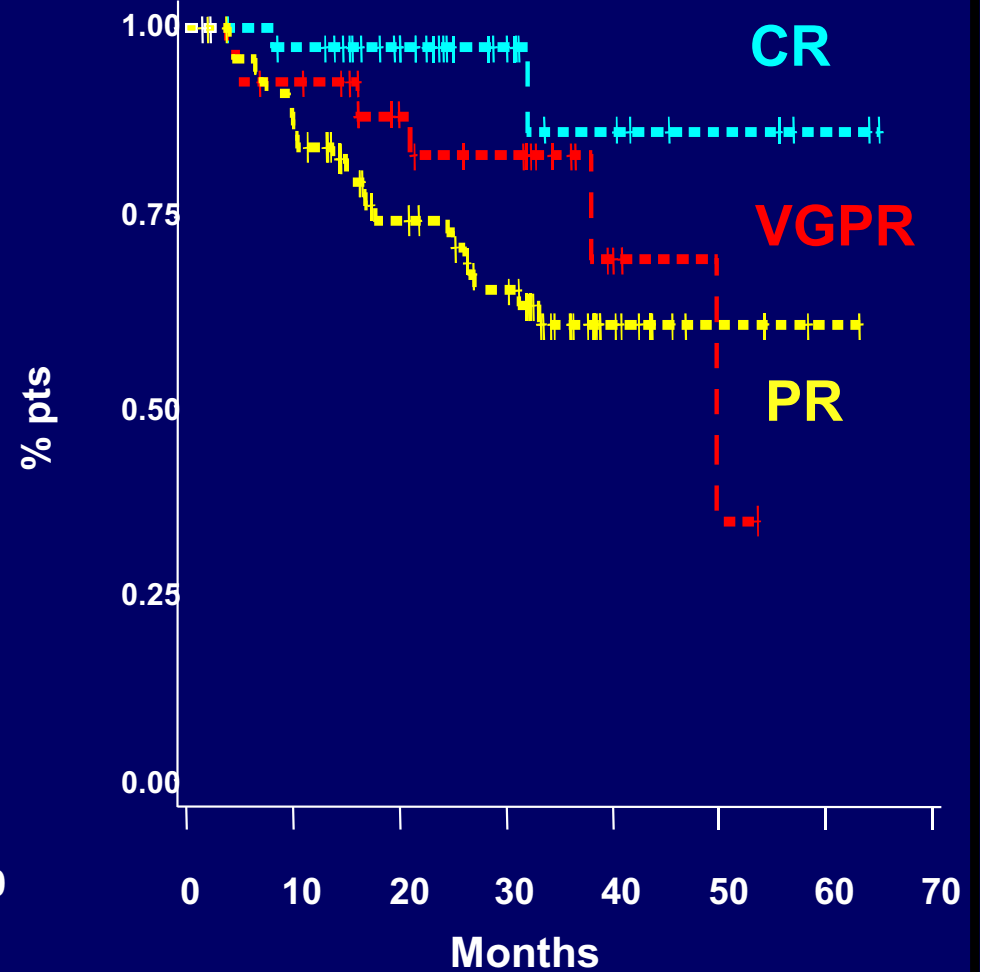


CR Predicts Long-term Outcome Age > 75 Years

PFS

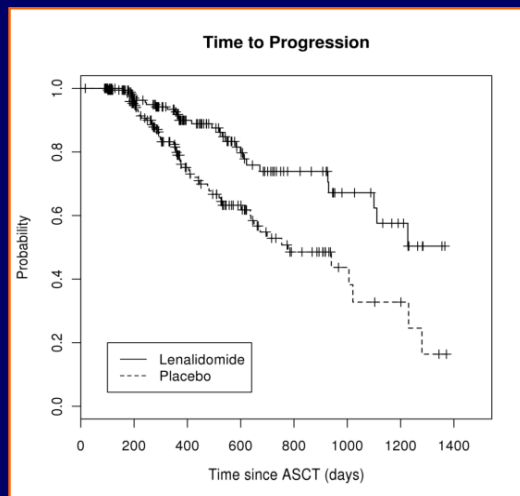


OS

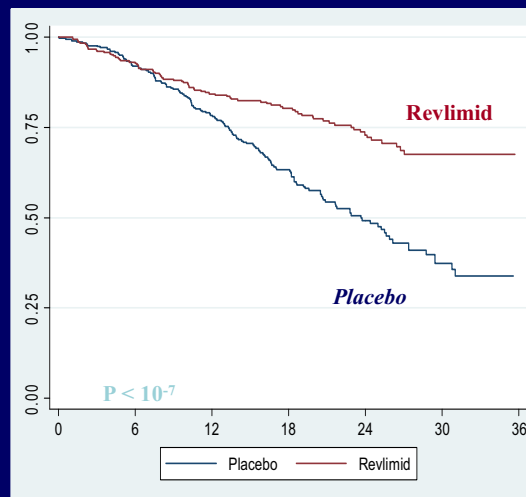


Outcome and continuous treatment

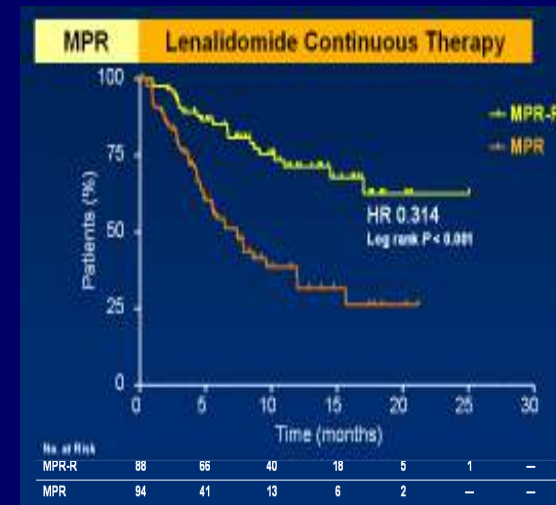
Lenalidomide maintenance



McCarthy *et al.* ASCO 2010

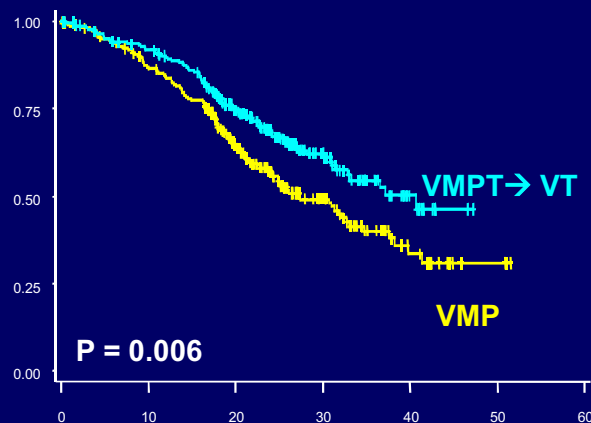


Attal *et al.* ASCO 2010

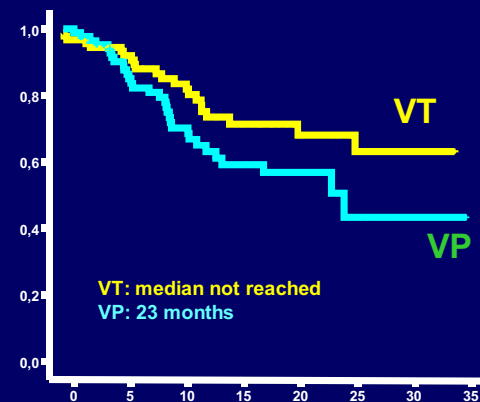


Palumbo *et al.* EHA 2010

Bortezomib maintenance



Palumbo *et al.* ASH 2009



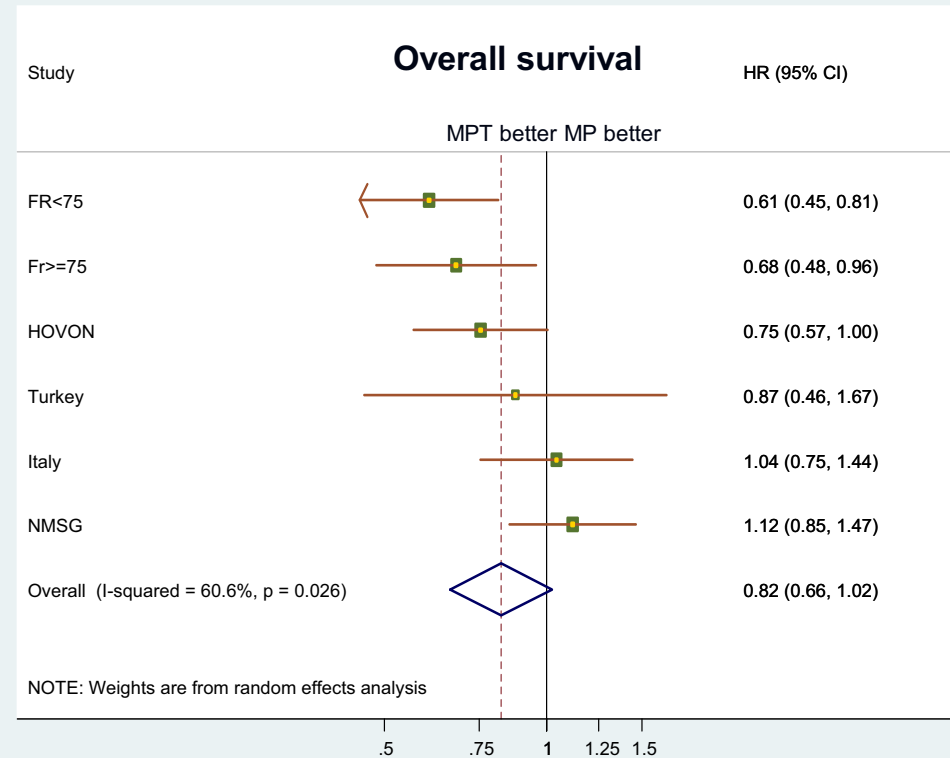
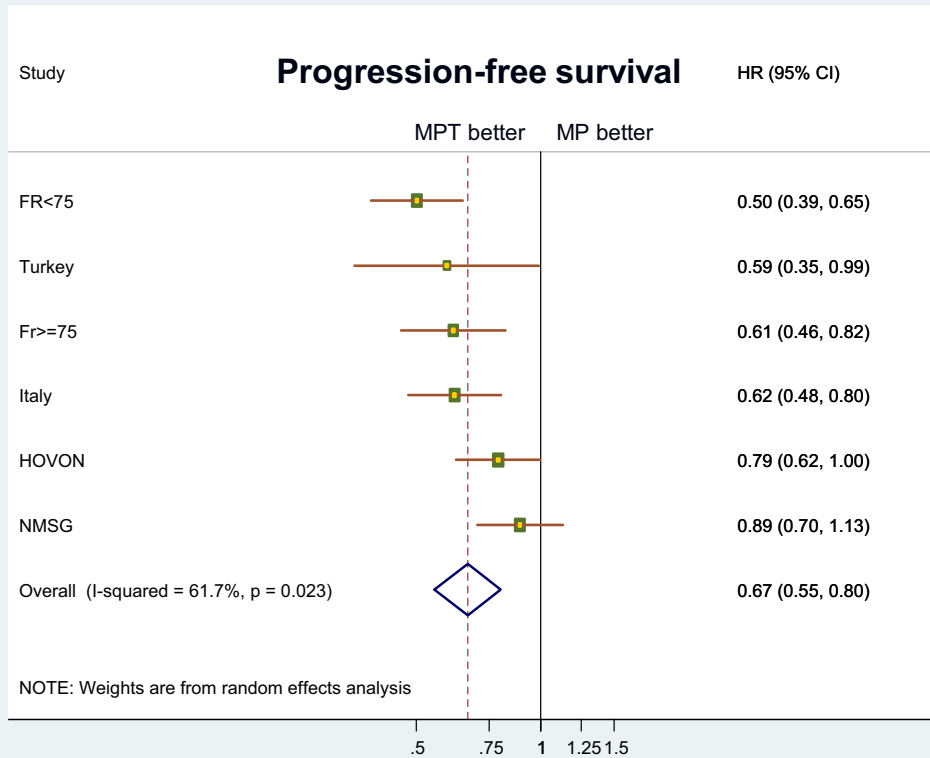
Mateos *et al.* ASH 2009

Dose-intensity in elderly patients efficacy-toxicity ratio

	Combination	Single agent
Discontinuation %		
65 - 75 years	17	10
> 75 years	34	16
Dose intensity %		
65 - 75 years	88	97
> 75 years	56	97

**Standard of Care
for
Elderly Patients**

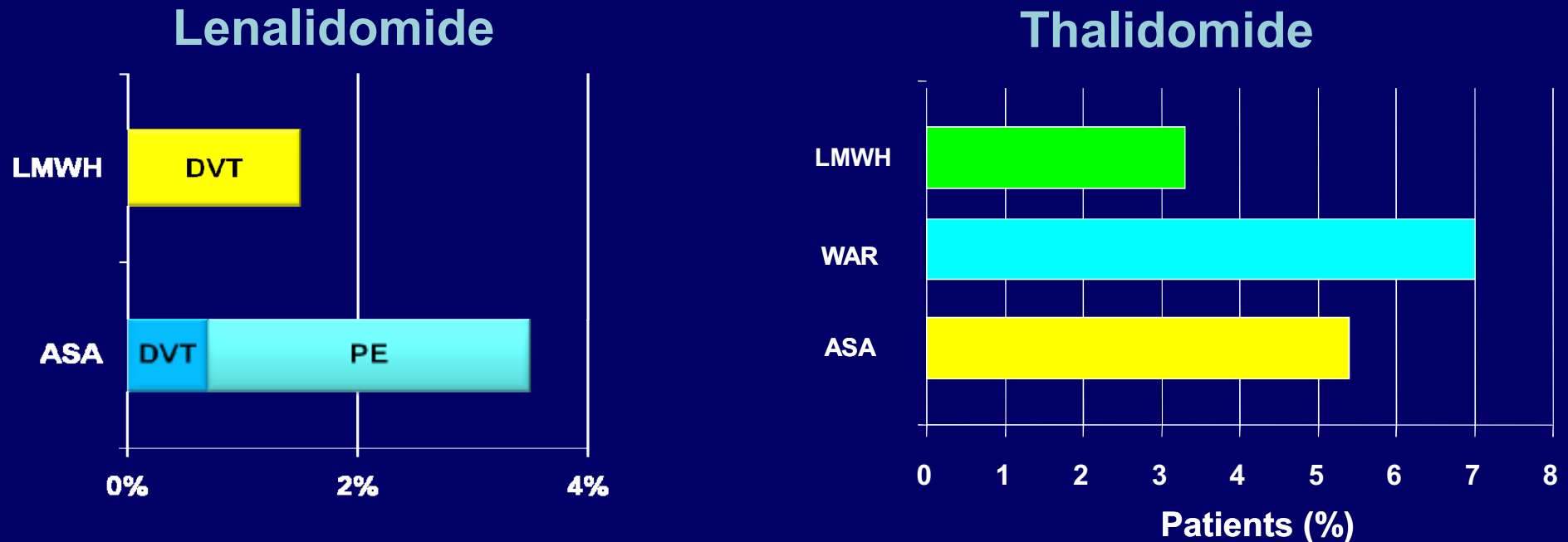
Meta-Analysis: MPT vs MP



MPT: melphalan-prednisone-thalidomide; MP: melphalan-prednisone

LMWH vs Warfarin vs Aspirin for Lenalidomide and Thalidomide

Standard Risk of VTE



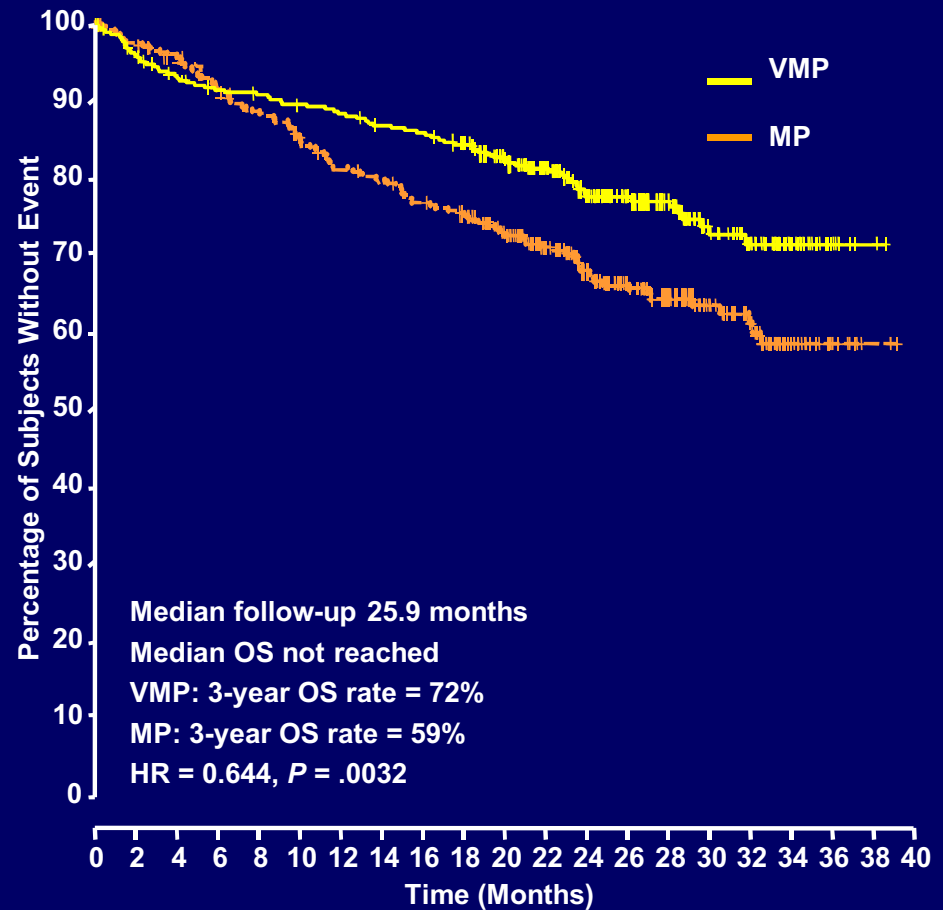
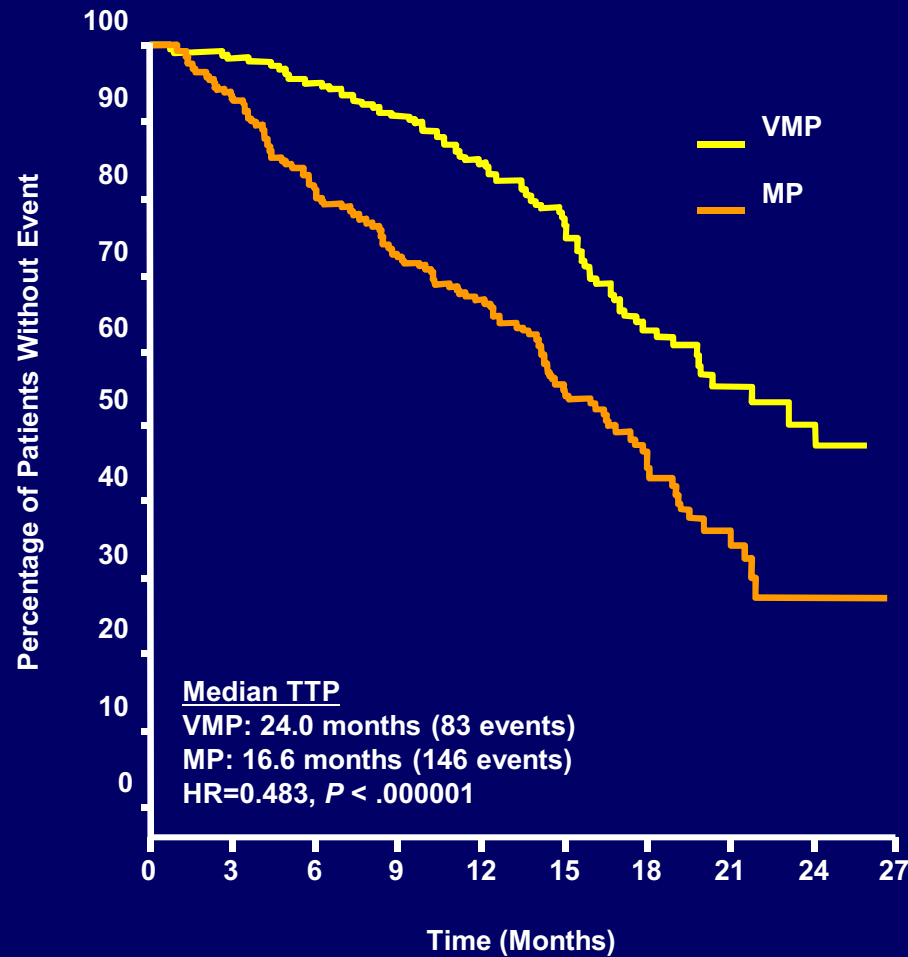
High Risk of VTE

- Previous VTE, infection, immobilization, CVC, doxorubicin
- LMWH is suggested

ASA: Acetylsalicylic acid; LMWH: low molecular weight heparin; VTE: venous thromboembolism;
CVC: central venous catheter

VMP (Bortezomib/Melphalan/Prednisone) Current Standard of Care

~52% reduced risk of progression
~36% reduced risk of death



Bortezomib: Once Weekly

	VMP (VISTA)	VMP twice-weekly	VMP once-weekly
CR	30%	27%	23%
2-year PFS	48%	56%	58%
Sensory PN			
Any grade	44%	44%	22%
Grade 3/4	13%	14%	2%
Discontinuation due to PN	na	16%	4%
Total planned dose	67.6 mg/m²	67.6 mg/m²	46.8 mg/m²
Total delivered dose	na	40.1 mg/m²	39.4 mg/m²

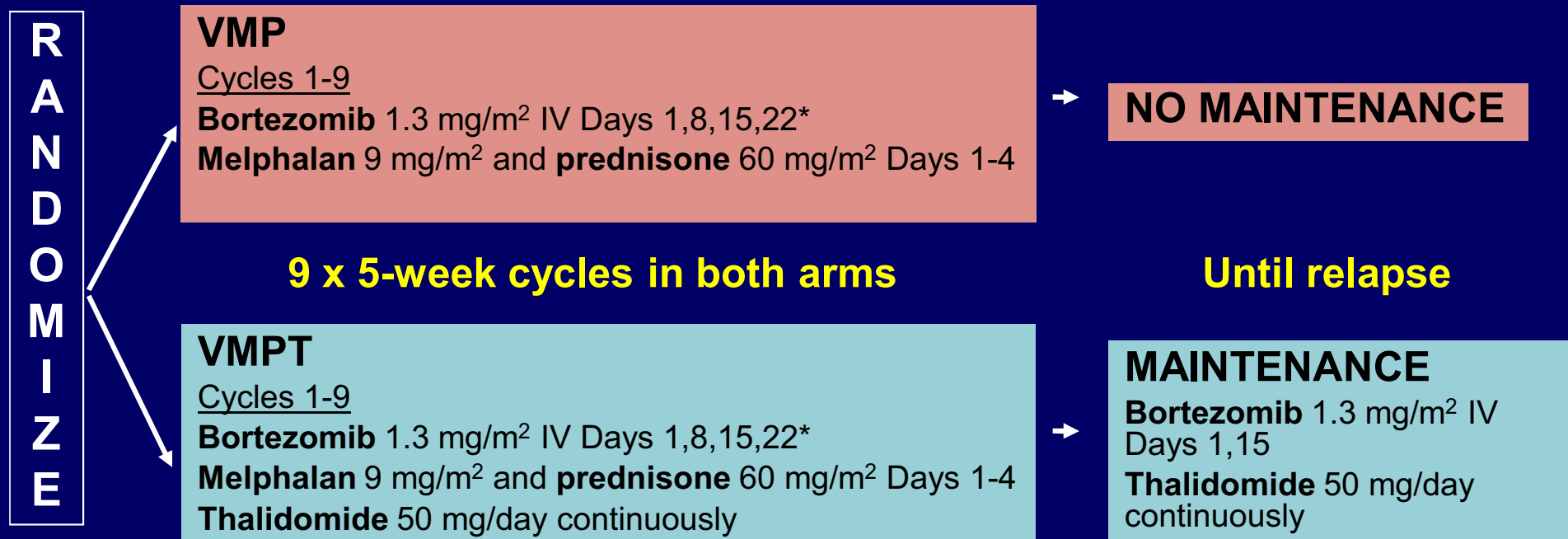
New treatment options

Bortezomib-Melphalan-Prednisone-Thalidomide VMPT-VT vs VMP

511 patients (older than 65 years) randomized from 61 Italian centers

Patients: Symptomatic multiple myeloma/end-organ damage with measurable disease

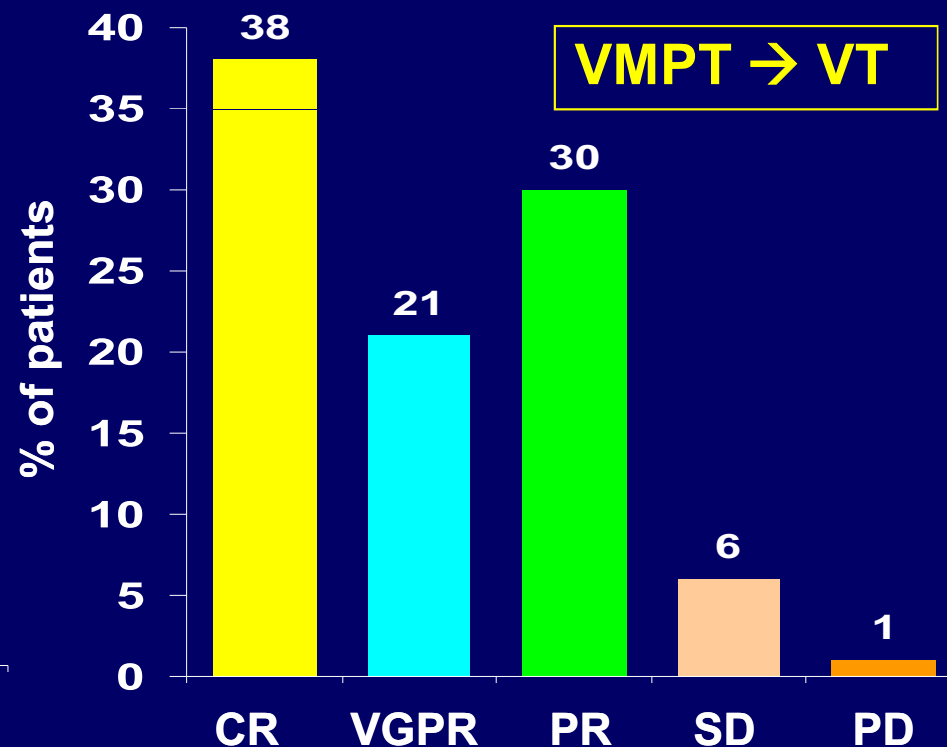
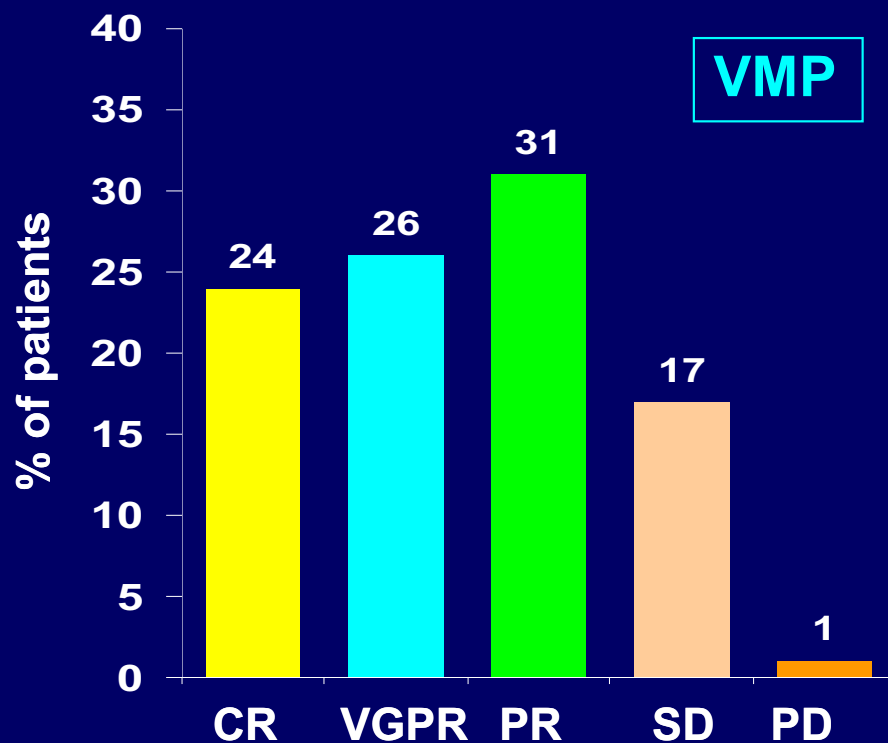
≥ 65 yrs *or* < 65 yrs and not transplant-eligible; creatinine < 2.5 mg/dL



*66 VMP patients and 73 VMPT-VT patients were treated with twice weekly infusions of bortezomib

Bortezomib-Melphalan-Prednisone-Thalidomide Response Rate

	VMP (N=253)	VMPT → VT (N=250)	P Value
CR	24%	38%	.0008
≥ VGPR	50%	59%	.03
≥ PR	81%	89%	.01

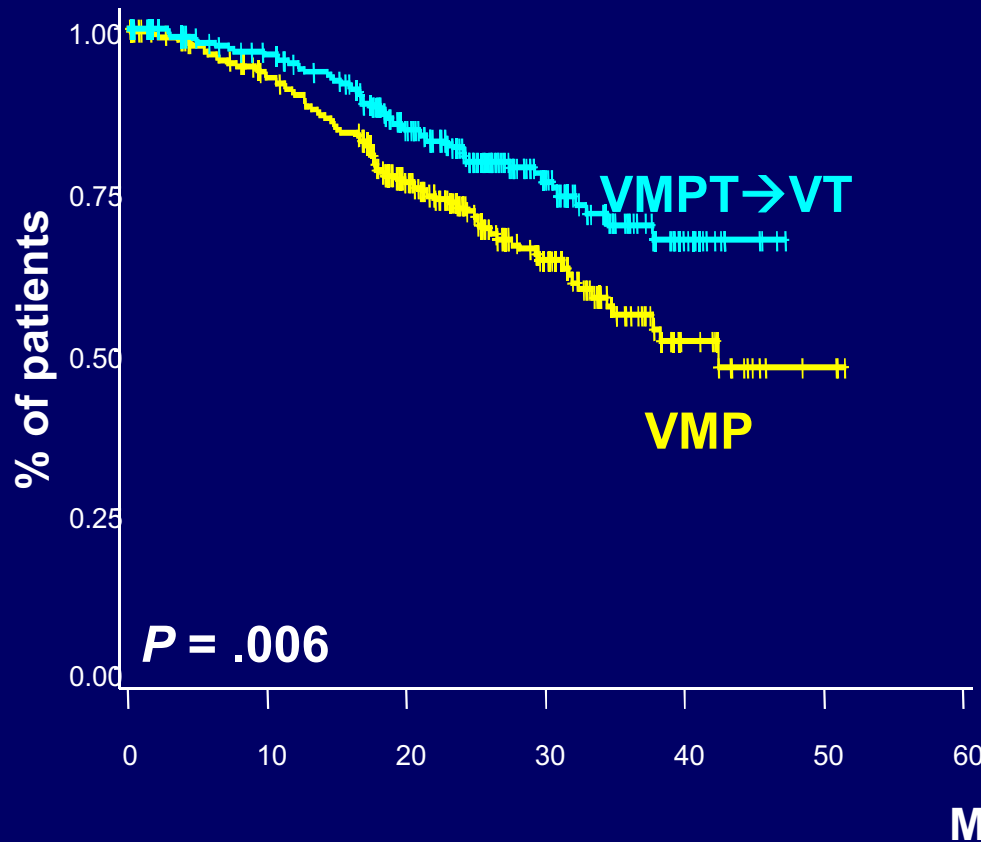


Bortezomib-Melphalan-Prednisone-Thalidomide

Median follow-up: 26.5 months

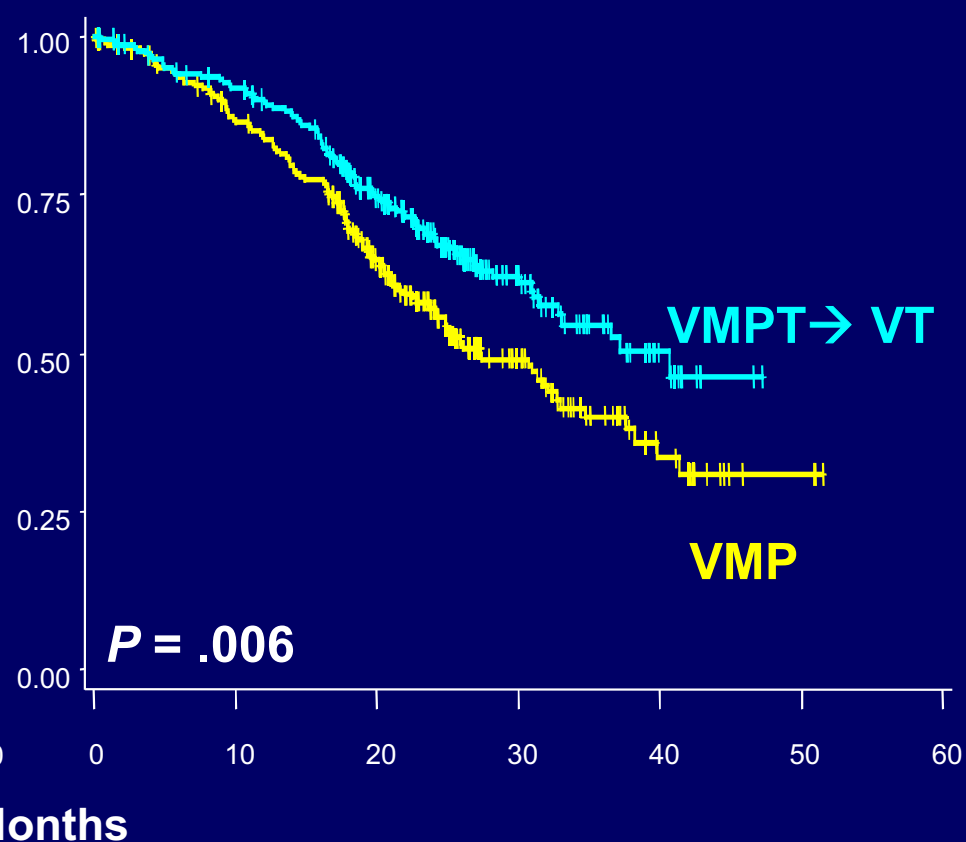
Time to next therapy

VMP: TTNT @ 3 years = 60%
VMPT → VT: TTNT @ 3 years = 72%



Progression-free survival

VMP: PFS @ 3 years = 41%
VMPT → VT: PFS @ 3 years = 56%



Bortezomib-Thalidomide Maintenance Phase III PETHEMA/GEM Study

Time-to-event data

Survival from first randomization:
median follow-up: 32 months

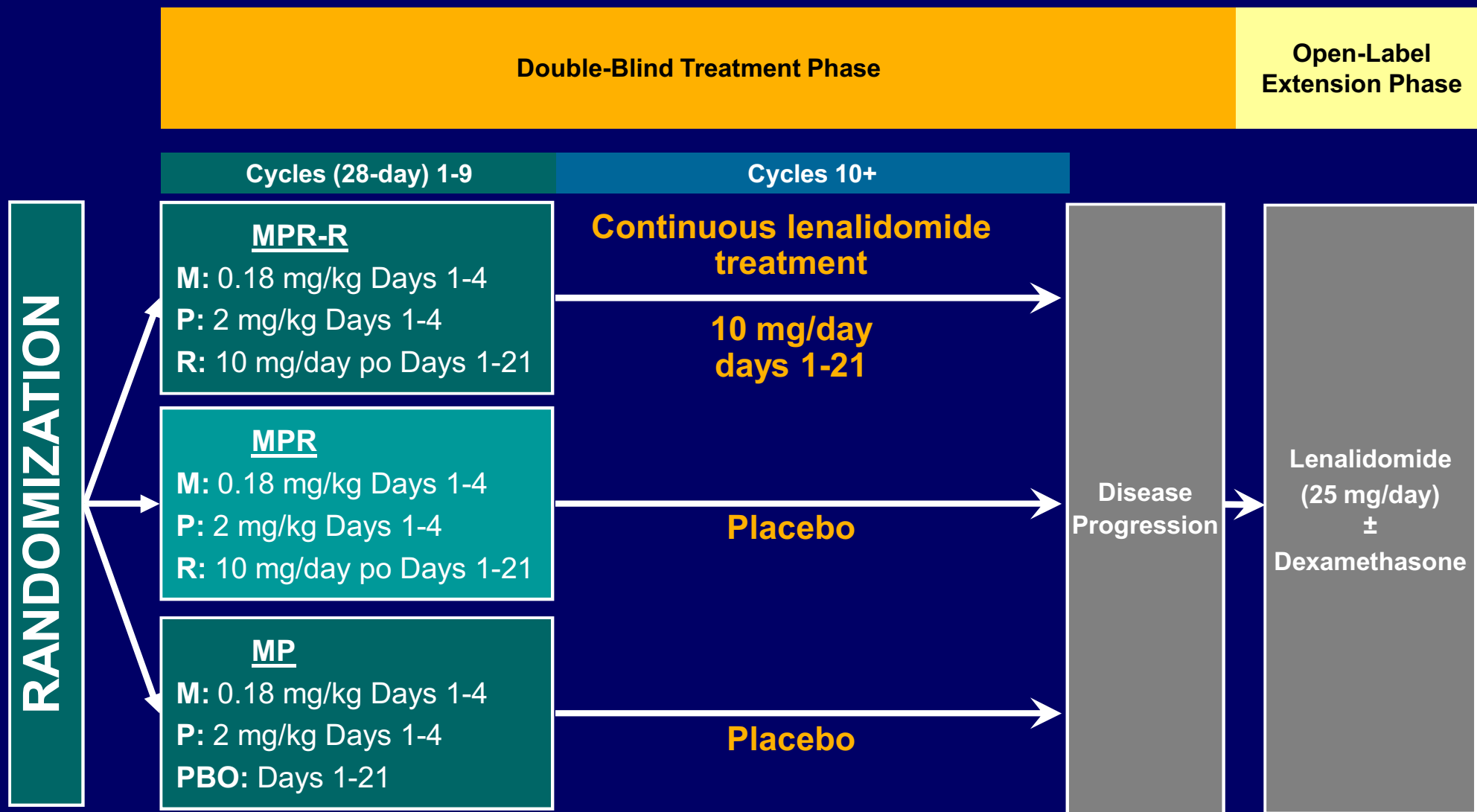
	VMP	VTP	<i>P</i>
Median PFS	34 months	25 months	.10
3-year OS	74%	65%	.30

Survival from second randomization:
median follow-up: 22 months

	VT	VP	<i>P</i>
Median PFS	32 months	24 months	.10
2-year OS	86%	81%	.7

Melphalan-Prednisone-Lenalidomide

N = 45,982 centers in Europe, Australia, and Israel



Stratified by age (≤ 75 vs > 75 years) and stage (ISS I/II vs III)

M, melphalan; P, prednisone; R, lenalidomide; PBO, placebo; po, orally; ISS, International Staging System.

Palumbo A, et al. EHA 2010. Abstract 0566.

Melphalan-Prednisone-Lenalidomide Response Rate

Best overall response ^a	MPR-R N = 152	MPR N = 153	MP N = 154	P Value (MPR-R vs MP)
ORR (≥ PR), %	77	68	50	< .001
CR ^b , %	16	11	4	< .001
≥ VGPR ^c , %	32	33	12	< .001
PR, %	45	35	38	—
SD, %	18	26	46	—
Median time to first response, months	2	2	3	< .001

^a As measured using EBMT criteria (*Bladé J, et al. Br J Haematol. 1998;102:1115-1123*)

^b Immunofixation negative with or without bone marrow confirmation

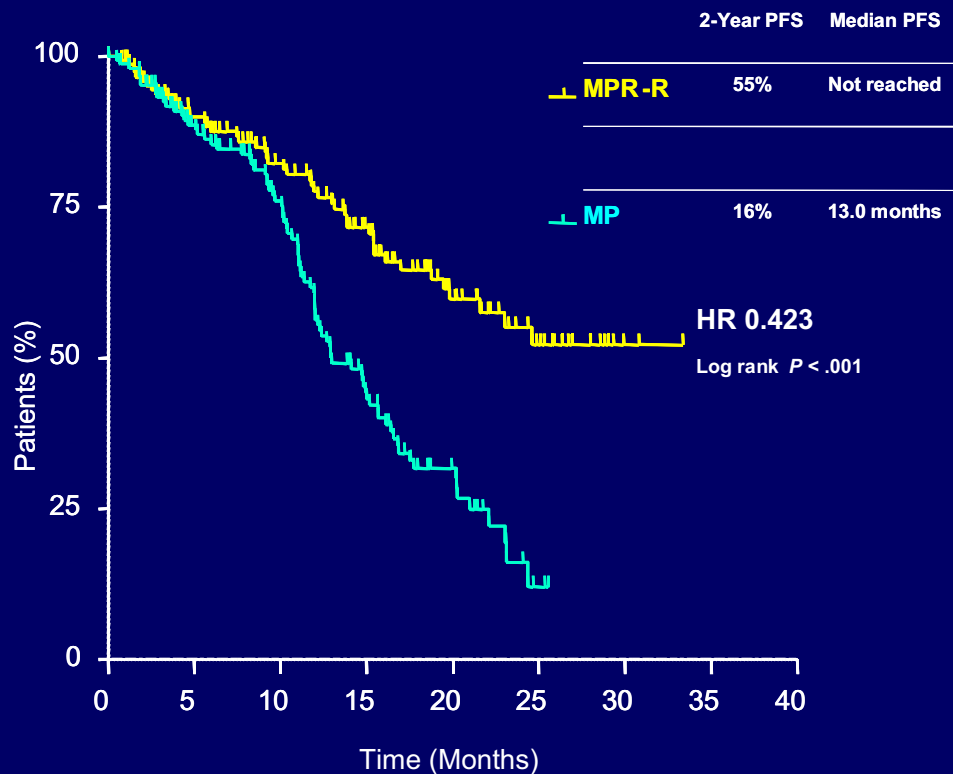
^c VGPR: > 90% reduction in M-protein

ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease

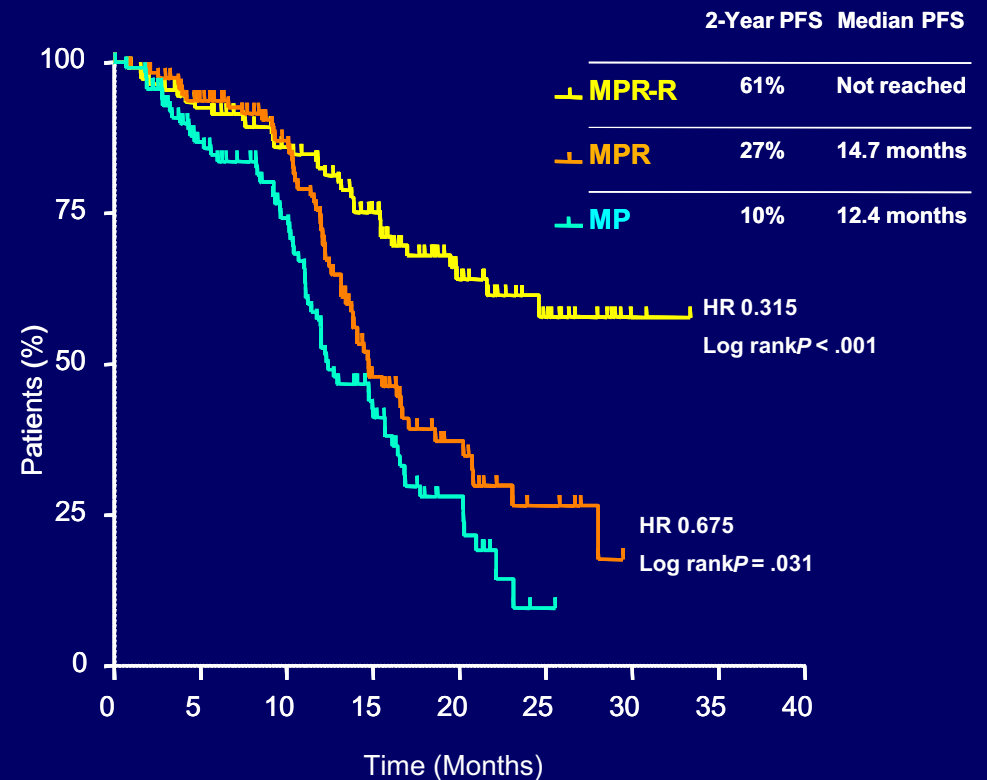
Palumbo A, et al. EHA 2010. Abstract 0566.

Melphalan-Prednisone-Lenalidomide Progression-Free Survival

58% Reduced Risk of Progression



65-75 Years of Age



MPR-R: melphalan-prednisone-lenalidomide lenalidomide continuous treatment;
MPR: melphalan-prednisone-lenalidomide; MP: melphalan-prednisone

Melphalan-Prednisone-Lenalidomide Treatment – Initial 9 Cycles

	MPR ^a	MP
Discontinuation rate^b, %		
65-75 years of age	17	10
> 75 years of age	34	16
Cumulative dose intensity^c, %		
65-75 years of age	88	97
> 75 years of age	56	97

^a MPR includes MPR-R and MPR for the initial 9 cycles.

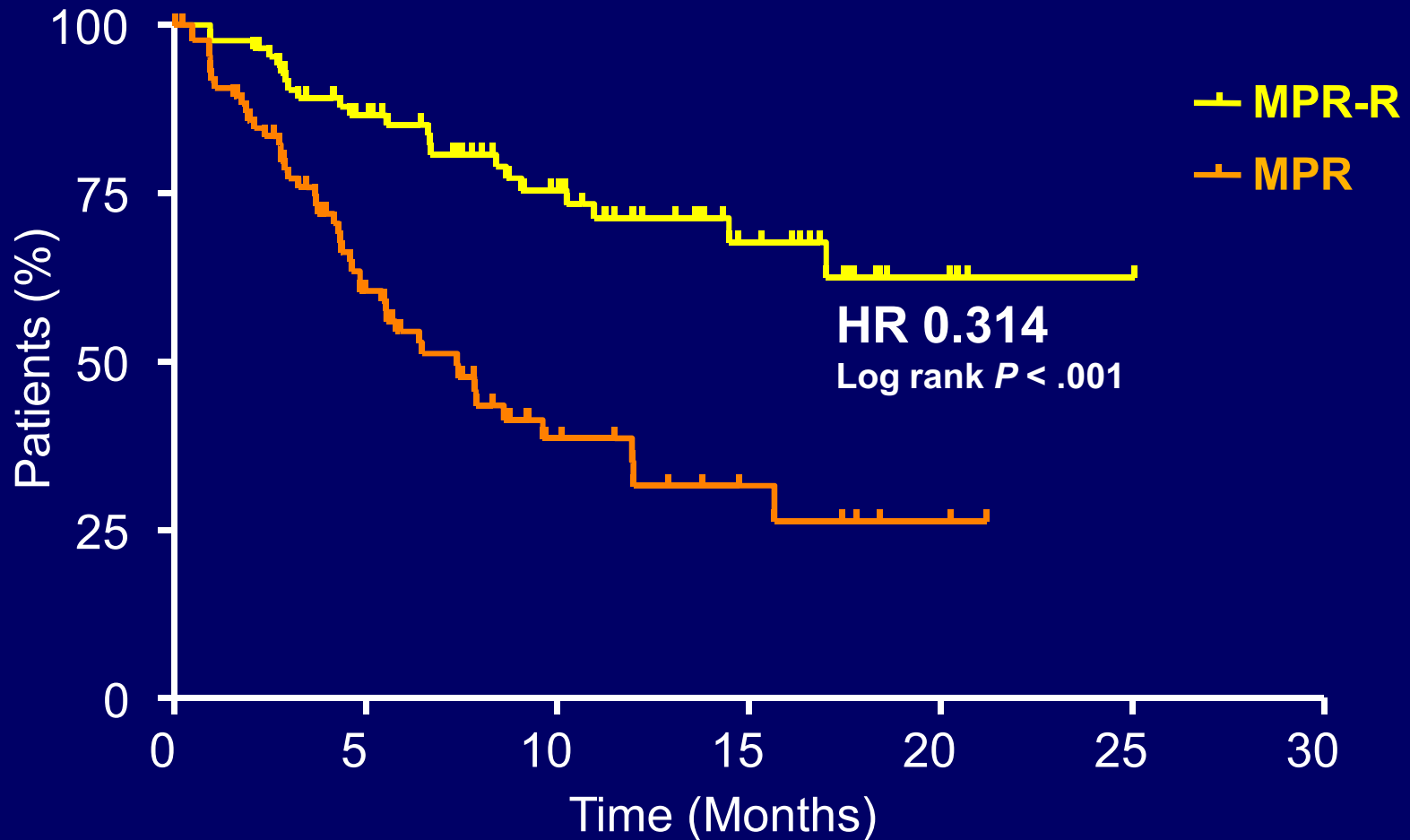
^b Discontinuation due to AEs or withdrawal of consent

^c Cumulative dose intensity of melphalan and lenalidomide/placebo

Melphalan-Prednisone-Lenalidomide Landmark Analysis 69% Reduced Risk of Progression

MPR

Lenalidomide Continuous Therapy



MPR-R: melphalan-prednisone-lenalidomide lenalidomide continuous treatment;
MPR: melphalan-prednisone-lenalidomide

Lenalidomide-Prednisone Melphalan-Prednisone-Lenalidomide

Cycles (28-day) 1-4

RP

R: 25 mg/d, days 1-21

P: 50 mg 3 times/week

Cycles (28-day) 5-10

MPR

M: 2 mg 3 times/week

P: 50 mg 3 times/week

R: 10 mg/d, days 1-21

M, melphalan; P, prednisone; R, lenalidomide;

Melphalan-prednisone-lenalidomide

(melphalan 0.18 → 0.13 mg/kg)

	RP	MPR ¹ 0.13 mg/kg	MPR ² 0.18 mg/kg MM015
Age	75(65-88)	75 (65-86)	71 (65-87)
GR 4 Adverse events %			
Neutropenia	6	11	36
Thrombocytopenia	0	0	13
G-CSF Administration	14	26	66
Response Rates			
VGPR	18	33	32

M, melphalan; P, prednisone; R, lenalidomide;

¹Falco P. et al. SIES 2010 (abstract 102)

²Palumbo A. et al. EHA 2010 (abstract 0566)

Age-Adjusted Therapy

INCIDENCE:

2002

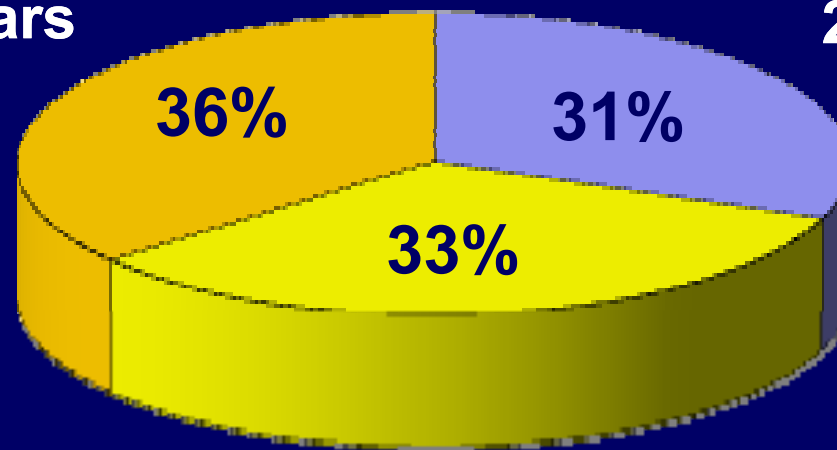
8.9/100.000

**Full-dose
chemotherapy**

65-74 years

**Autologous
transplant**

25-64 years



75-101 years

**Reduced-dose
chemotherapy**

Are all the elderly the same?

