How to treat elderly patients: combination therapy or sequencing

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Disclosures for Palumbo Antonio, MD

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Age-Adjusted Therapy

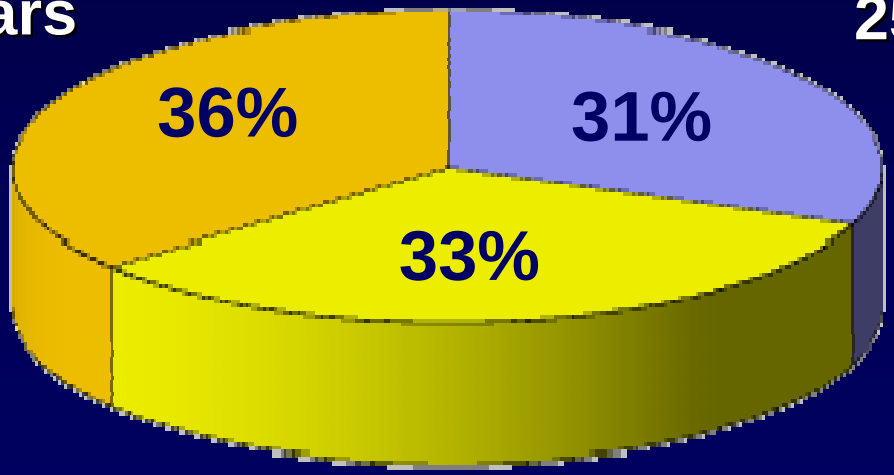
INCIDENCE: **2002** **8.9/100.000**

Full dose chemotherapy

65-74 years

Autologous transplant

25-64 years



75-101 years

Reduced-dose chemotherapy

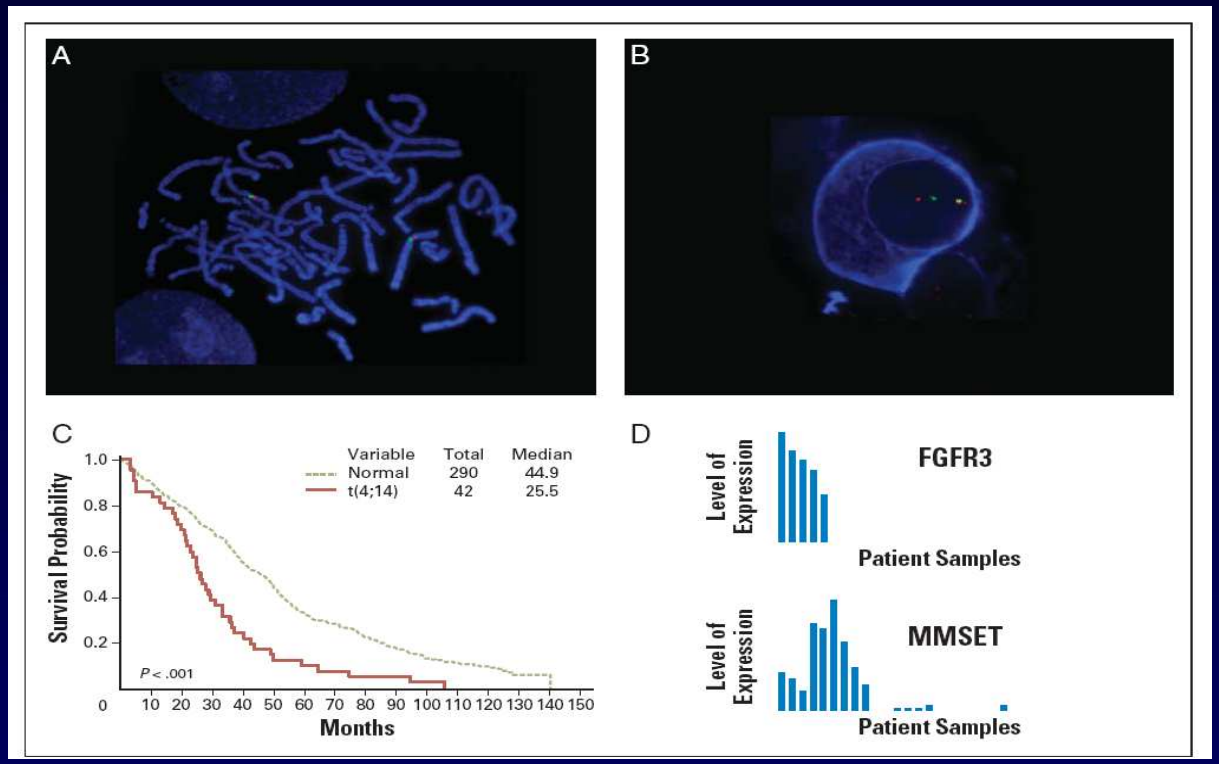
Regione Piemonte, Assessorato Sanità 2006

Criteria for Diagnosis/ Start therapy

- **Serum and/or urine monoclonal protein**
- **> 10% Bone marrow monoclonal plasma cells**
  biopsy proven plasmocytoma
- **Myeloma-related organ dysfunction (1 or more)**
  (C) Hypercalcemia (Ca > 10.5 mg/L or ULN)
  (R) Renal insufficiency (creatinine >2 mg/ dL)
  (A) Anemia (Hb < 10 g/ dL or 2 g< normal)
  (B) Bone disease
- **Doubling M- component in less than 2 months**

Kyle RA et al. Leukemia (2009) 23, 3-9

Cytogenetic Data



Minimum panel required:

t (4;14), t (14;16), 17p13 deletion

More comprehensive panel:

t (11;14), chromosome 13 deletion, chromosome 1 abnormalities, hyperdiploid

Fonseca R et al. *Leukemia* (2009), 1-12

Open question

Treatment paradigm for patients in VGPR:

- **Stop treatment:**

  No 2° transplantation

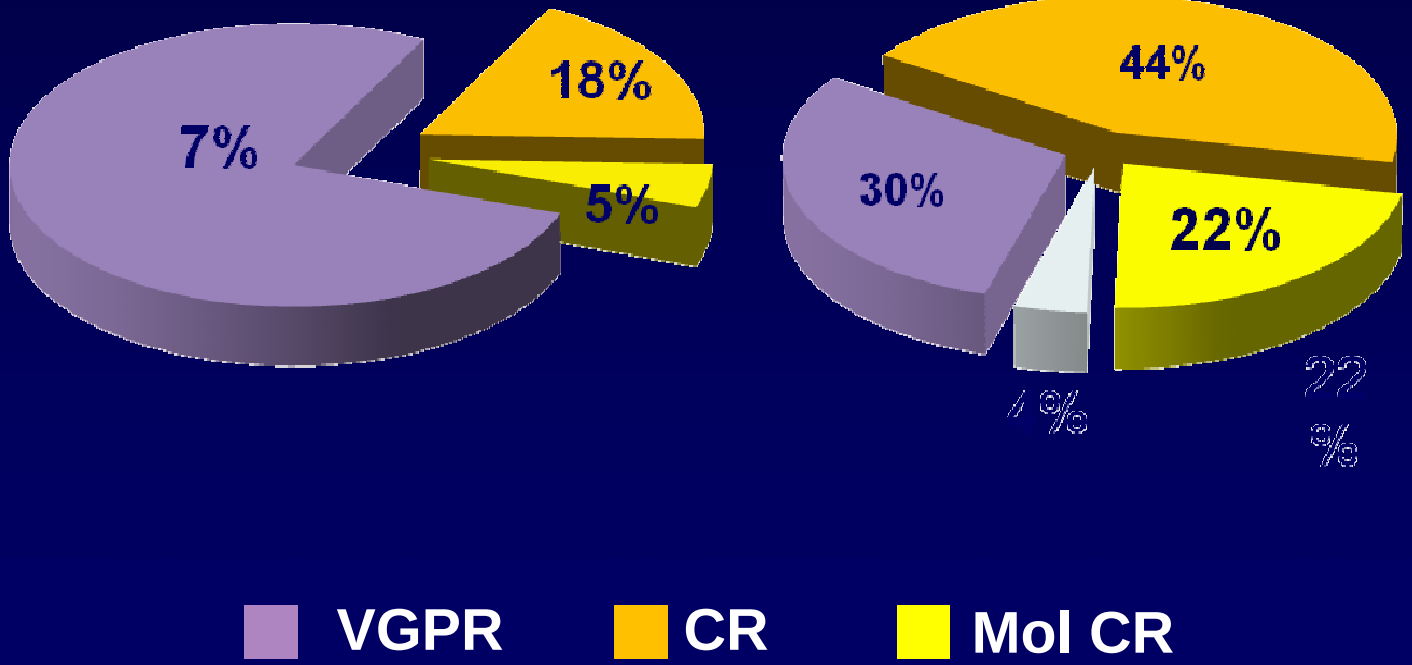
  No consolidation / maintenance

- **Is this right??**

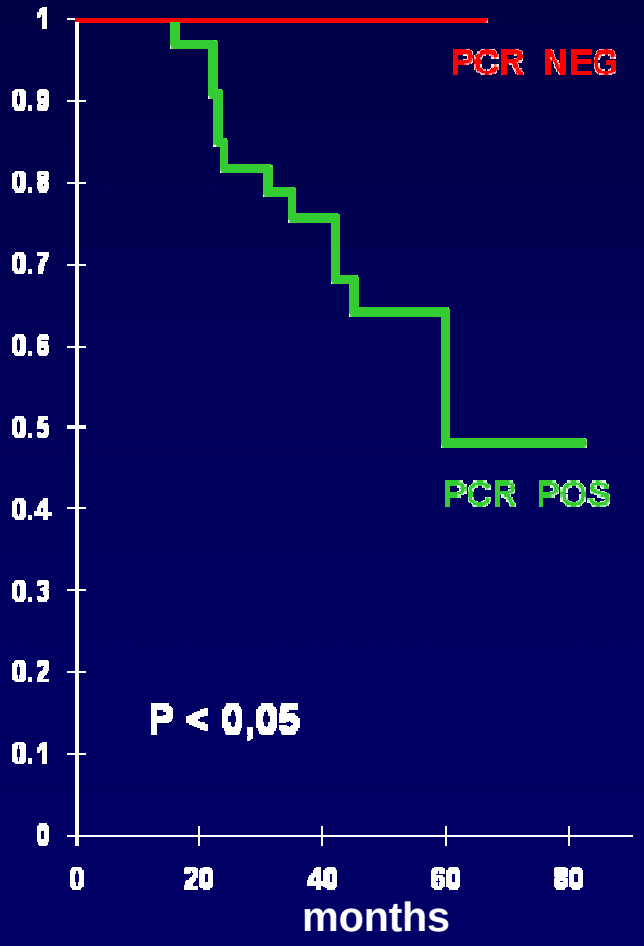
Bortezomib-Thalidomide-Dexamethasone consolidation in VGPR patients

Responses after ASCT
VGPR 100%
CR 22%

Responses after VTD
VGPR 100%
CR 66%



PFS in PCR negative patients



Ladetto et al. *J Clin Oncol* 2009 in press

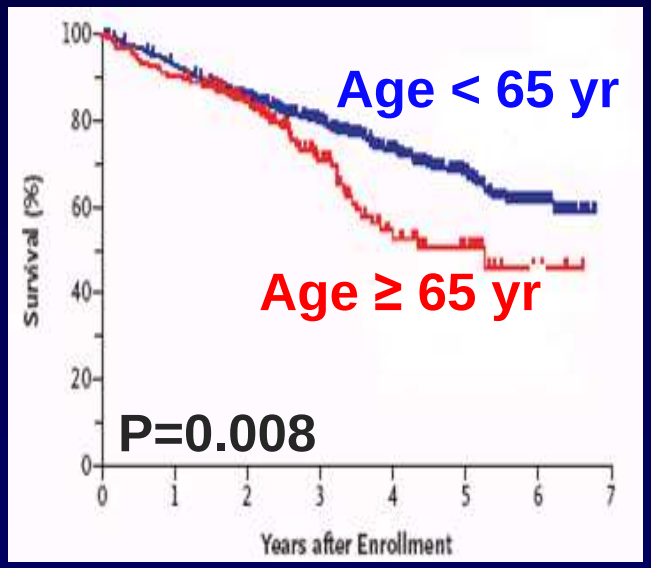
Autologous stem cell transplantation

for elderly patients

Autologous Stem Cell Transplantation in Elderly Patients

Survival Advantage

Age <65 years

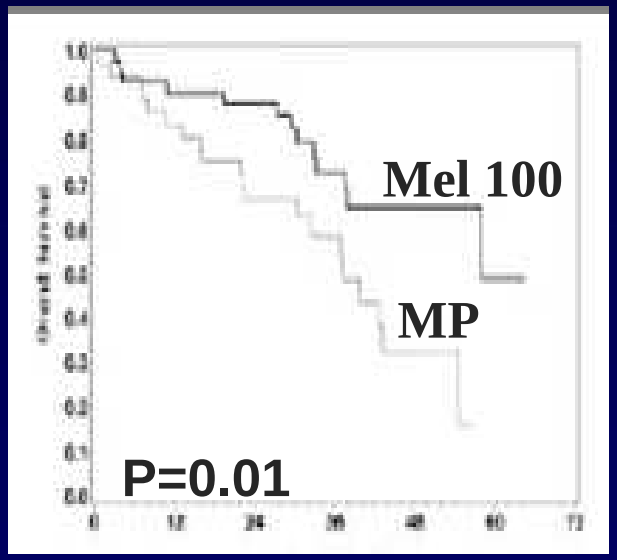


Tandem MEL200

Barlogie B, et al. *N Engl J Med.* 2006;354(10):1021-1030.

Survival Advantage

Age 65-70 years

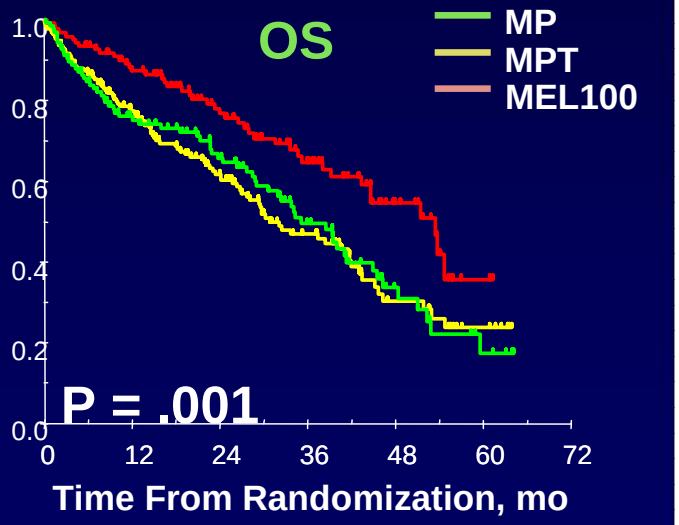


Tandem MEL100

Palumbo A, et al. *Blood.* 2004;104: 3052-3057.

NO Survival Advantage

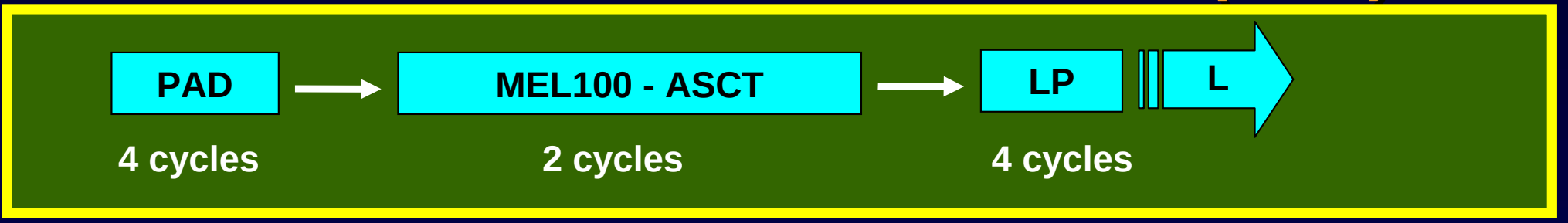
Age 65-75 years

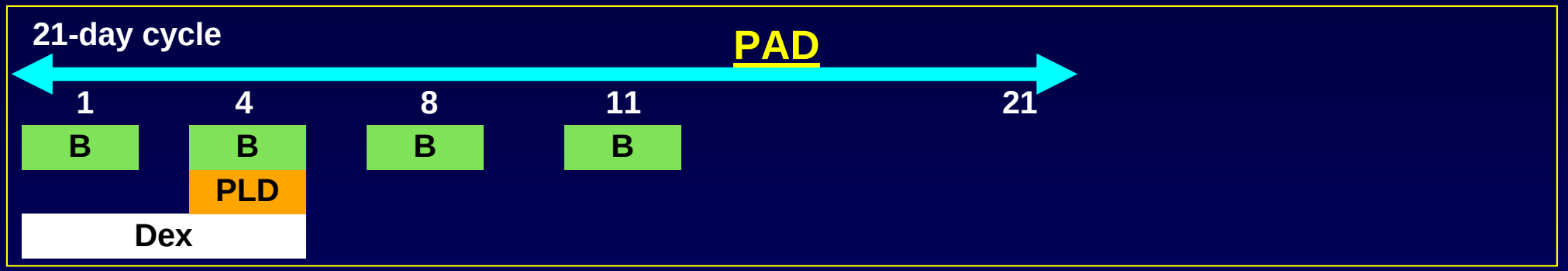


Tandem MEL100

Facon T, et al. *Lancet.* 2007;370(9594):1209-1218.

Bortezomib based induction (PAD) autologous stem cell transplantation Lenalidomide based maintenance (LP-L)



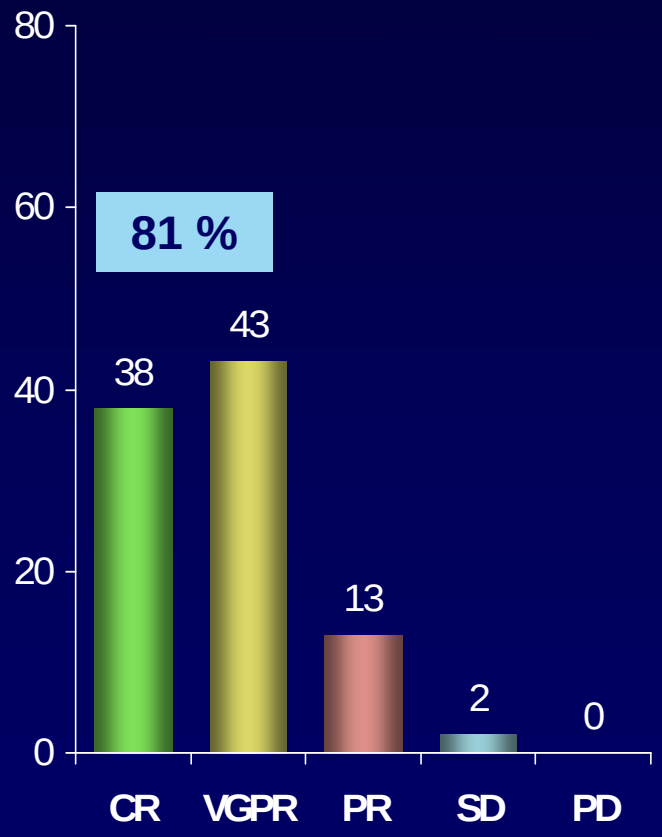


PAD: Bortezomib+ Doxorubicin+ Dexamethasone; MEL-100: Melphalan 100 mg/m^2 ; LP: Lenalidomide+ Prednisone; L: Lenalidomide: B: Bortezomib; PLD: Pegylated liposomal doxorubicin; Dex: Dexamethasone

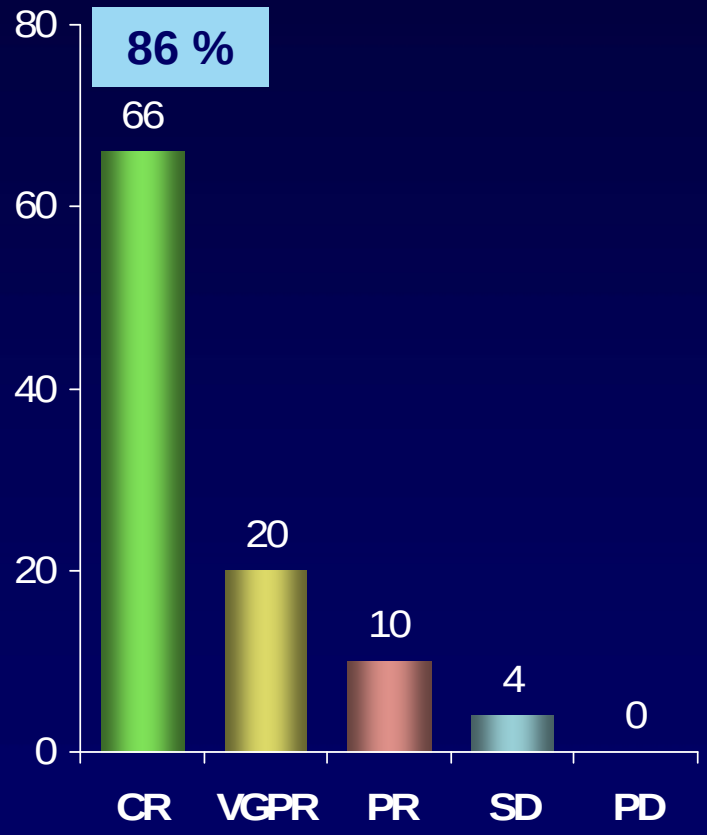
Palumbo A, et al. *J Clin Oncol.* 2009 in press

Role of Maintenance After Autologous Transplant

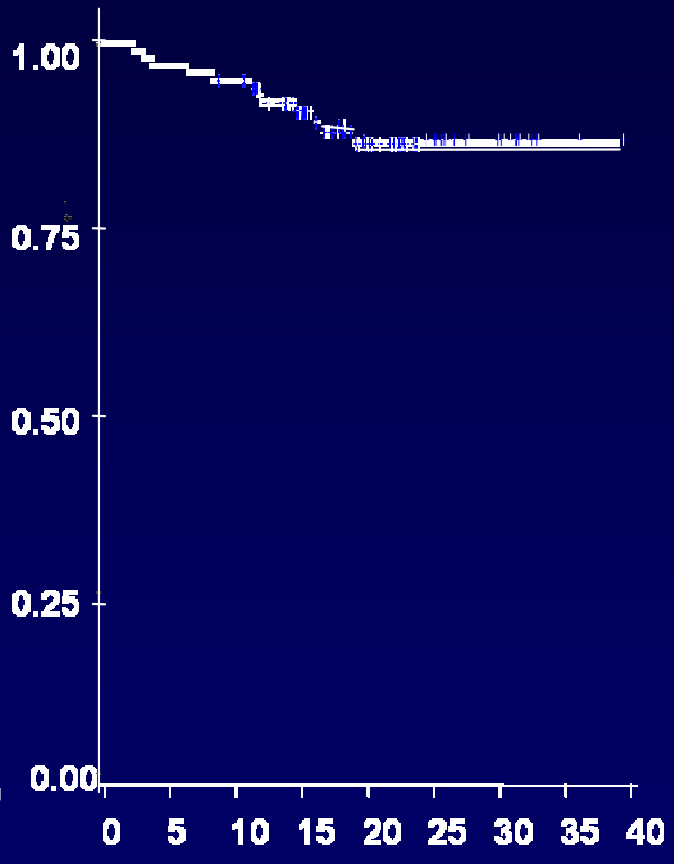
PAD-MEL100* n=83



MEL100-LP-L* n=50



OS



* Per protocol

Palumbo A, et al. *J Clin Oncol.* 2009 in press

Standard of care for elderly patients

MPT (melphalan/prednisone/thalidomide) Current Standard of Care

MPT vs MP Studies

	Median PFS, Months	PFS *P Value*	Median OS, Months	OS, *P Value*
IFM [1]	27.5 vs 17.8	<.0001	51.6 vs 33.2	.0006
GIMEMA[2]	N/A	.0006	N/A	NS
IFM [3]	24.1 vs 19	.001	45.3 vs 27.7	.03
Nordic[4]	16 vs 14	NS	29 vs 33	NS
Hovon[5]	N/A	<.001	N/A	NS

N/A= not available; N.S.= not significant

1. Facon T, et al. *Lancet*. 2007;370(9594):1209-1218. 2. Palumbo A, et al. *Lancet*. 2006;367(9513):825-831. 3. Hulin C, et al. *Blood*. 2007;110: Abstract 75. 4. Waage A, et al. *Blood*. 2007;110: Abstract 78. 5. Wijermans P, et al. *Haematologica*. 2008;93: Abstract 0440.

LMWH vs Warfarin vs Aspirin for Thalidomide Induction Regimens

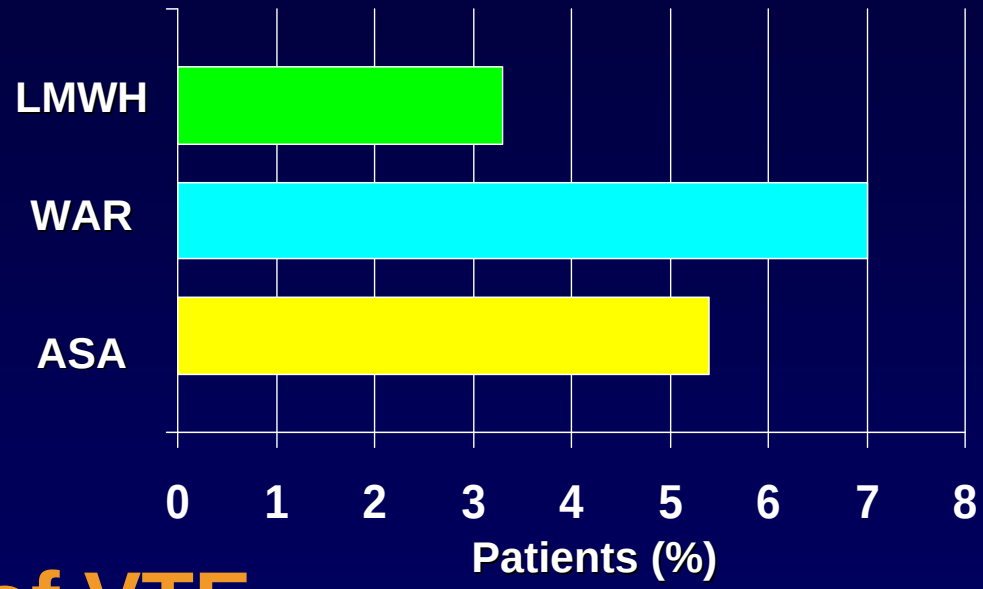
Standard Risk of VTE

Study Design

Thalidomide regimens (950 pts) Random

- **ASA** Aspirin 100 mg/day
- **WAR** Warfarin 1.25 mg/day
- **LMWH** Enoxaparin 40 mg/day

Risk of VTE



High Risk of VTE

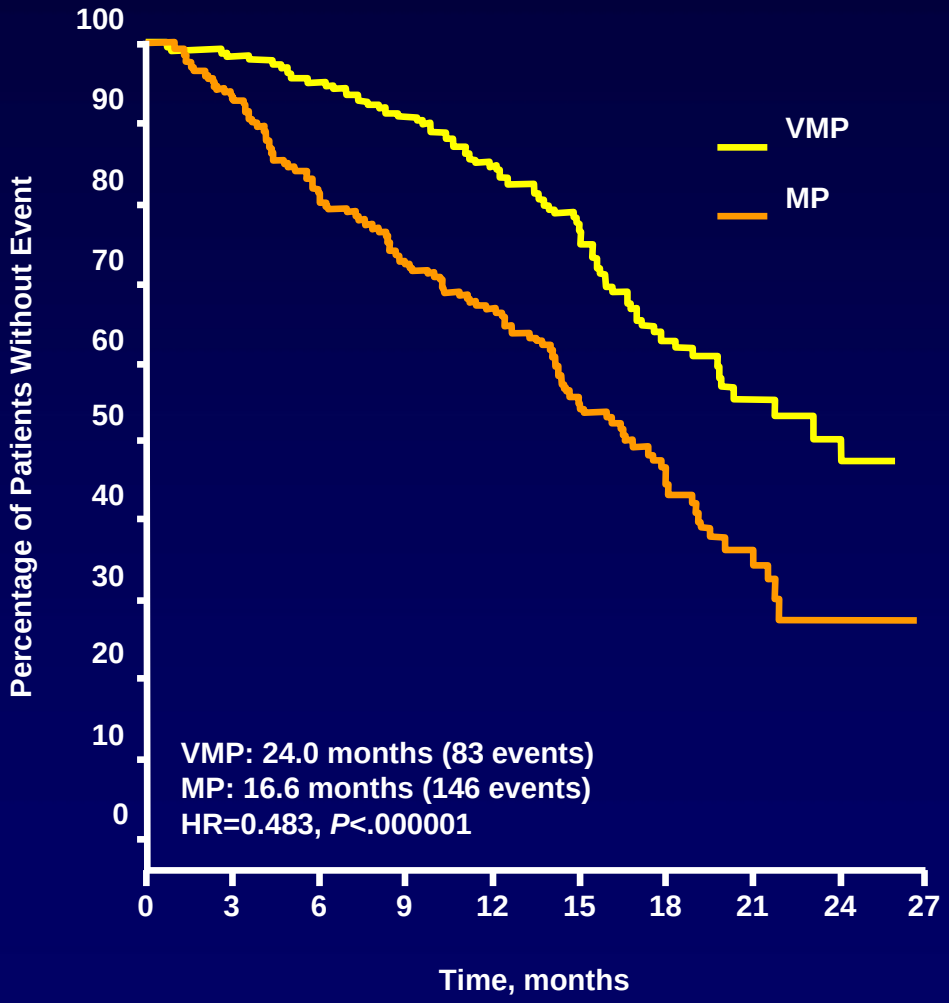
- previous VTE, infection, immobilization, CVC, doxorubicin
- LMWH is suggested

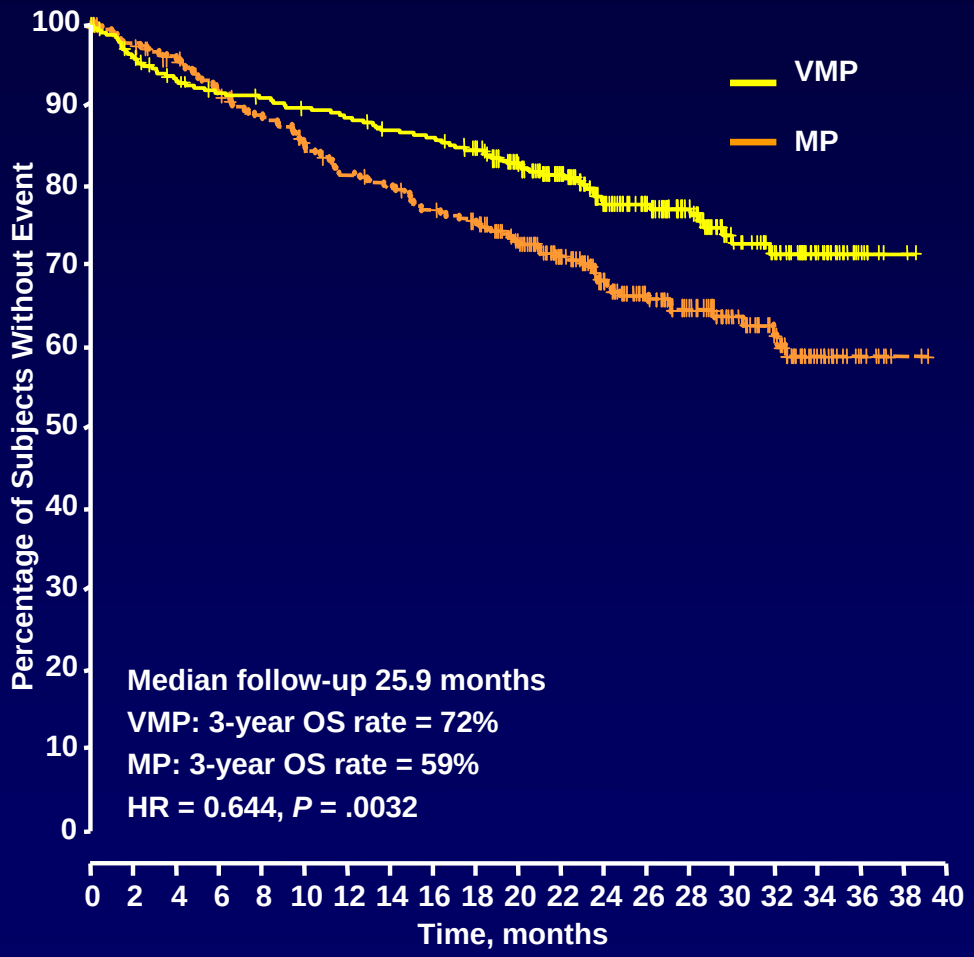
ASA: Acetylsalicylic acid; LMWH: low molecular weight heparin; VTE: venous thromboembolism; CVC: central venous catheter

Palumbo , et al. EHA 2009; Abs 0214.

VMP (bortezomib/melphalan/prednisone) Current Standard of Care

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





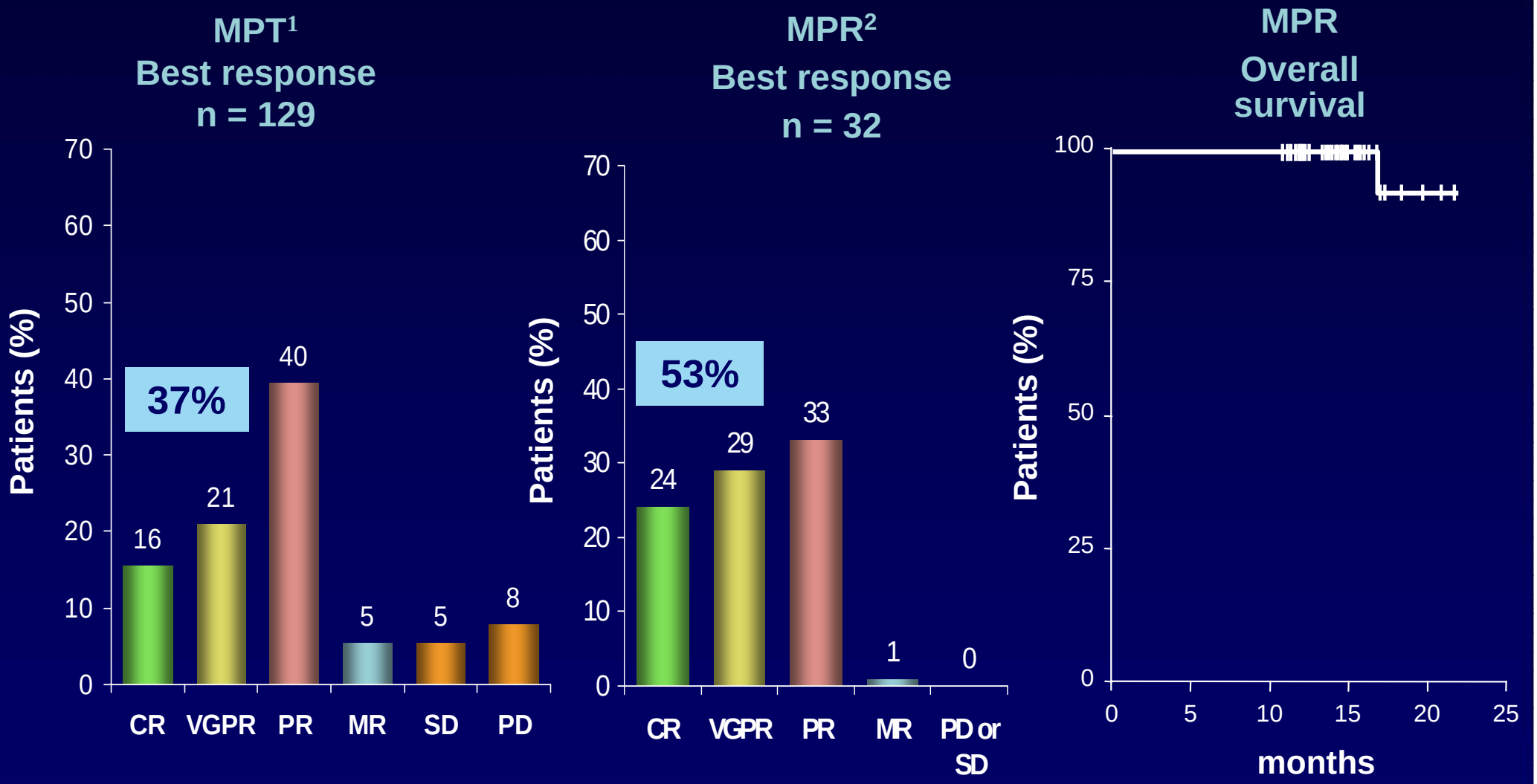
San Miguel JF, et al. *N Engl J Med*. 2008;359(9):906-917.

VMP (bortezomib/melphalan/prednisone) bortezomib: twice or once weekly infusion

	VMP Twice weekly (N=344) GIMEMA[1]	VMP weekly (N=130) PETHEMA[2]	VMP weekly (N=177) GIMEMA[3]
CR	30%	22%	20%
2- year PFS	50%	74%	70%
Peripheral neuropaty	13%	5%	2%
Discontinuation	24%	8%	4%

1.San Miguel JF et al. Phase III Vista Trial. *Blood* 2008; 112:650; 2. Mateos MV et al *Blood* 2008; 112: 651; 3. Palumbo A. et al. *Blood* 2008; 112: 652

MPT (melphalan/prednisone/thalidomide) vs MPR (melphalan/prednisone/lenalidomide)



1. Palumbo A, et al. *Lancet*. 2006;367(9512):825-831.
2. Palumbo A, et al. *J Clin Oncol*. 2007;25(28):4459-6445.

Treatment choice

Efficacy

MPT/MPR*	VMP§
Standard risk	High risk
Older	Younger

Safety

MPT*	MPR*	VMP§
Cytopenia	Neuropathy	DVT
Oral	Oral	Renal insufficiency

*MPT: melphalan/prednisone/thalidomide; MPR: melphalan/prednisone/lenalidomide;
§MPV: melphalan/prednisone/bortezomib; VTE: venous thromboembolism.

Future options

Combination therapy:

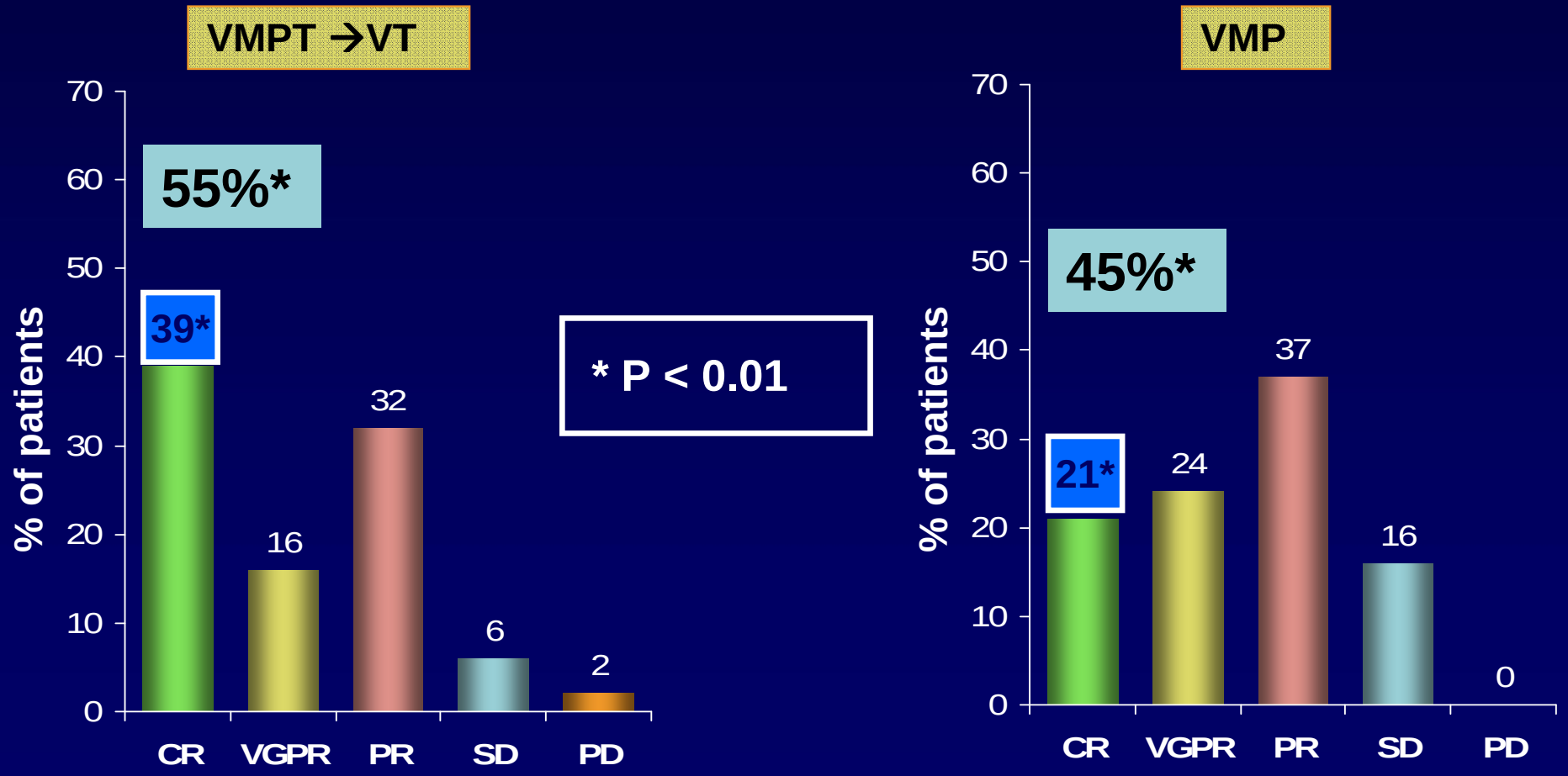
- **4 drug combination to increase response**
- **Maintenance to improve remission duration**

Phase III randomized study: VMPT (bortezomib/melphalan/prednisone/thalidomide) versus VMP (bortezomib/melphalan/prednisone)

VMPT induction
Nine 5-week cycles
Bortezomib 1.3 mg/m^2 d 1 8 15 22
Melphalan, 9 mg/m^2 (d 1-4)
Prednisone 60 mg/m^2 (d 1-4)
Thalidomide 50 mg/day continuously

→

VT maintenance
4-week cycles until progression
Bortezomib 1.3 mg/m^2 d 1 15
Thalidomide 50 mg/d continuously



Palumbo A et al. Blood 2008;112:652

Future options

- Single agent
- Sequential approach
- Friendly approach

Novel agents as primary treatment safety

Grade 3 or 4 adverse events, %	IFM MPT	VISTA MPV	GIMEMA MPR	ECOG Rd
Neutropenia	48	40	52	19
Thrombocytopenia	14	37	24	5.5
Anaemia	14	19	5	7
Neuropathy	6	13	0	1.5
DVT	12	1	5	9
Infection	10	7	9.5	7
Herpes zoster	2.5	3	NR	NR

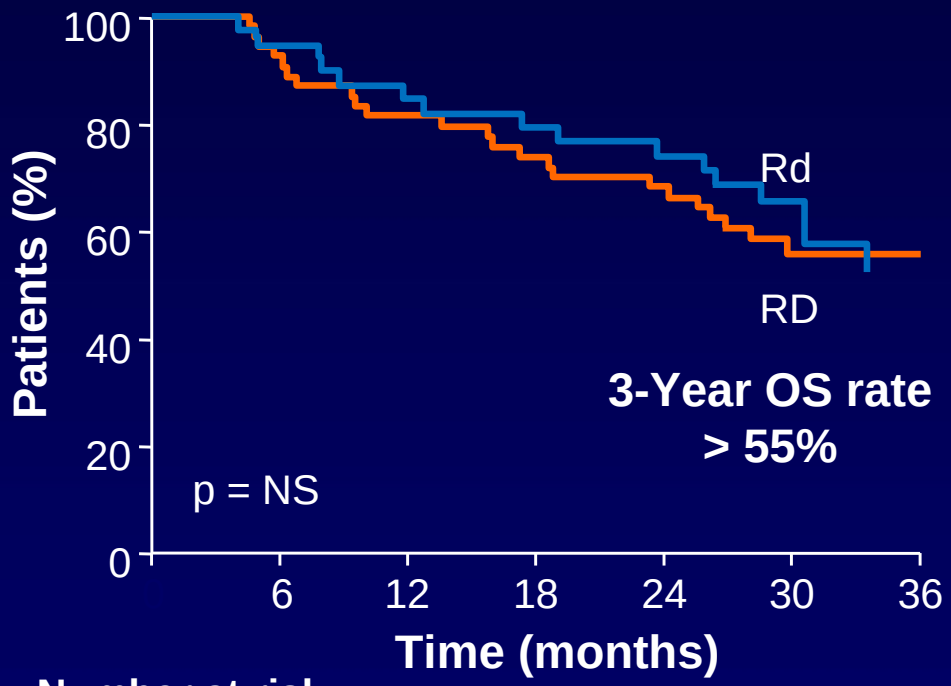
MPT: melphlan/prednisone/thalidomide; MPR: melphlan/prednisone/lenalidomide;
MPV: melphlan/prednisone/bortezomib; Rd: lenalidomide/low dose dexamethasone

Moreau P, et al. Blood Rev. 2008;22:303-9.

Continued treatment is associated with longer OS

Lenalidomide 25 mg d 1-21
Dexamethasone 40 mg d 1,8,15,22

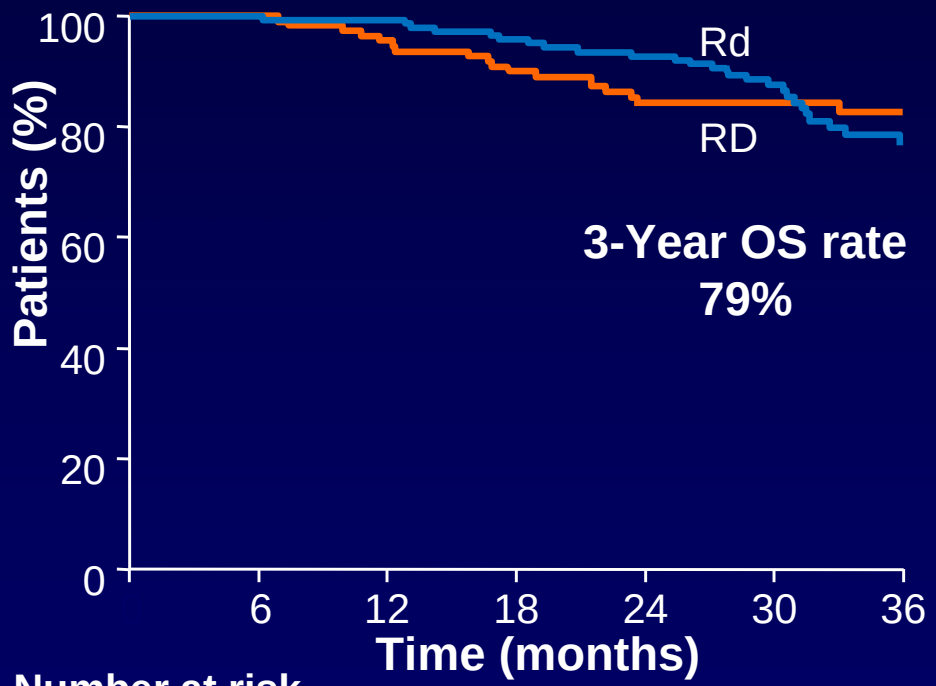
OS: 4 months treatment



Number at risk

RD	54	50	43	39	36	20	14
Rd	39	37	33	30	27	19	11

OS: 12 months treatment



Number at risk

RD	108	108	103	97	90	67	44
Rd	140	140	139	133	128	95	51

RD: Lenalidomide+ Dexamethasone; Rd: Lenalidomide + low dose dexamethasone

Rajkumar SV, et al. Joint ASH/ASCO symposium at ASH 2008.

Adjusted therapy

Full dose chemotherapy	Reduced dose chemotherapy

65-75 years

Normal:
- Cardiac
- Pulmonary
- Liver
- Renal function

>75 years

Normal:
- Cardiac
- Pulmonary
- Liver
- Renal function

<65 years

Abnormal:
- Cardiac
- Pulmonary
- Liver
- Renal function

65-75 years

Abnormal:
- Cardiac
- Pulmonary
- Liver
- Renal function

Recommendations by A. Palumbo.

Age-Adjusted Doses

	65-75 Years	>75 Years	Further Dose Redcution
Dexamethasone weekly	40 mg	20 mg	10 mg
Melphalan days 1-4	0.25 mg/kg	0.18 mg/kg	0.13 mg/kg
Thalidomide per day	200 mg	100 mg	50 mg
Lenalidomide* days 1-21	25 mg	15 mg	10 mg
Bortezomib	1.3 mg/m^2 Twice-weekly	1.3 mg/m^2 Weekly	1.3 mg/m^2 Twice-monthly

If a grade 3-4 AE occurs: 1. discontinue therapy; 2. wait for grade 1 AE; 3. restart at a lower dose

*Lenalidomide plus melphalan starting dose 10 mg/d

AE: adverses events

Recommendations by A. Palumbo.

Therapeutic Algorithm
Level of Evidence 1b (≥ 1 Randomized Trial)

MPT	>	MP	5 randomized trials
MPV	>	MP	1 randomized trial
MPR	>	MP	1 randomized trial

Other options

VMP → Bortezomib/thalidomide maintenance

VMPT → Bortezomib/thalidomide maintenance

Rd → Until progression