

Treatment of the Non-Transplant Patient With Multiple Myeloma

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Treatment Options for Multiple Myeloma

Choice depends on age, performance status, and whether high-dose chemotherapy (HDT) or stem cell rescue is planned

HDT planned

Vincristine + doxorubicin + dexamethasone (VAD)[‡] or VAD-based regimen (?)

Thalidomide + dexamethasone,^{* ‡} T-VAD,[‡] other combinations

Proteasome inhibitors (Bortezomib)-based regimens[‡]

IMiDs (lenalidomide, pomalidomide)

HDT not planned

Melphalan + prednisolone (MP)

Cyclophosphamide ± prednisolone^{*}

Melphalan + prednisolone + thalidomide (MPT)^{* ‡}

Melphalan + prednisolone + bortezomib (MPV)^{‡‡}

* Oral therapies.

‡ Suitable for patients with renal failure.

MPT vs MP in Elderly Patients With MM

Study	Regimen	N	CR (IF-)	TTP PFS/EFS	Overall Survival
Palumbo ¹	MPT (T maint.)	129	16%	21.8 mo	NS (45 mo vs 47.6 mo P = .79)
	MP (no maint.)	126	4%	14.5 mo	
Facon ²	MPT (72 weeks)	125	13%	27.5 mo	51.6 mo vs 33.2 mo HR = 0.59, P = .0006
	MP (72 weeks)	196	2%	17.8 mo	
Hulin ³	MPT (72 weeks)	113	7%	24.1 mo	45.3 mo vs 27.7 mo HR n/a, P = .03
	MP (72 weeks)	116	1%	19 mo	
Wijermans ⁴	MPT (T maint.)	165	2%	13 mo	40 mo vs 31 mo P = .05
	MP (no maint.)	168	2%	9 mo	
Gulbrandsen ⁵	MPT (T maint.)	363	6%	20 mo	NS (29 mo vs 33 mo P = .46)
	MP (no maint.)		3%	18 mo	

Abbreviation: NS, not significant.

1 Palumbo A, et al. *Blood*. 2008;112(8):3107-3114. 2. Facon T, et al. *Lancet*. 2007;370(9594):1209-1218.

3. Hulin C, et al. *J Clin Oncol*. 2009;27(22):3664-3670. 4. Wijermans P, et al. *J Clin Oncol*. 2010;28(19):3160-3166.

5. Gulbrandsen N, et al. *Haematologica*. 2008;93(Suppl 1): Abstract 0209.

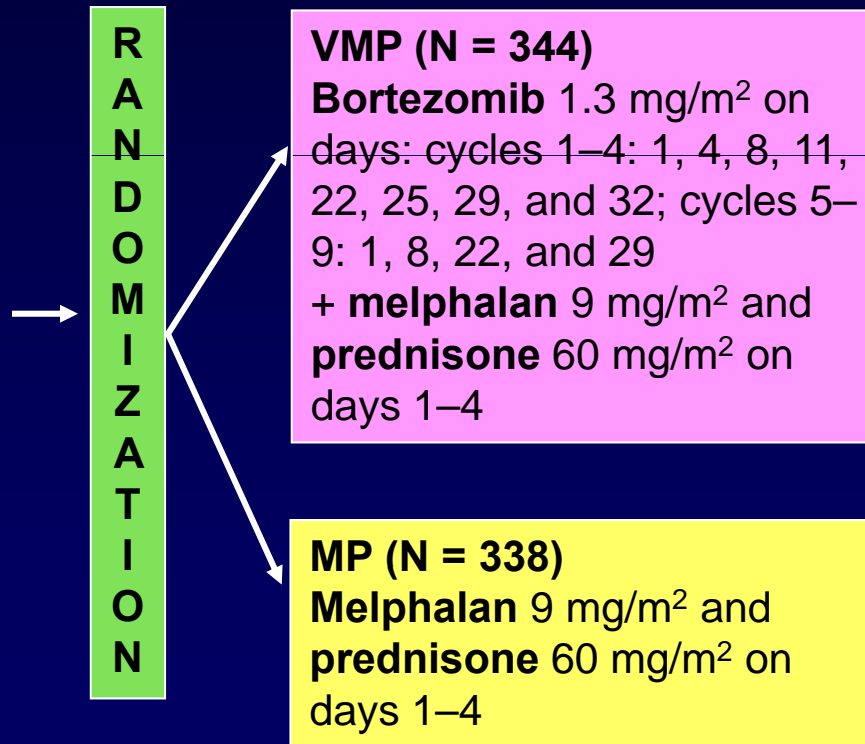
MP vs. MPT: Meta-analysis of 1,682 Individual Patient Data from 6 Randomized Clinical Trials

	MP (n = 868)	MPT (n = 814)	Hazard ratio	<i>P</i>
Median PFS	14.9 months	20.4 months	0.67 (0.55-0.80)	0.001
Median OS	32.7 months	39.3 months	0.82 (0.66-1.02)	0.085

Waage A, et al. *J Clin Oncol*. 2010;28(15S): Abstract 8130). Waage A, et al. *Haematologica*. 2010;95 (suppl 2): Abstract 567.

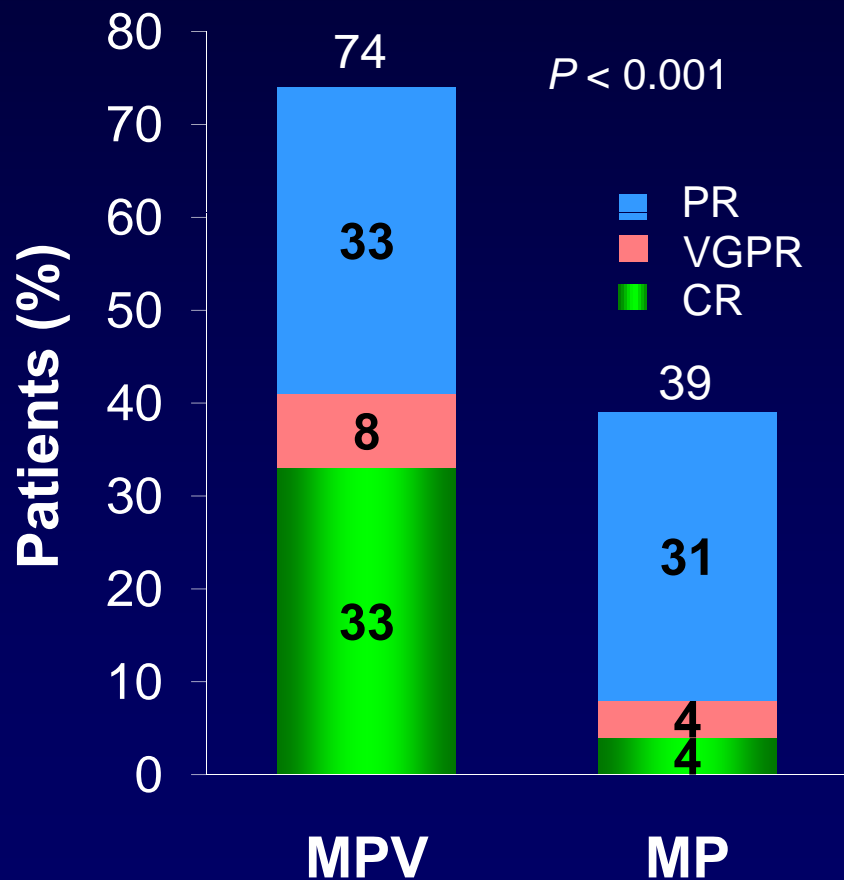
VISTA: Phase III Study of VMP vs MP in Previously Untreated Multiple Myeloma

682 untreated MM patients ineligible for HDT-SCT from 151 centers in 22 countries

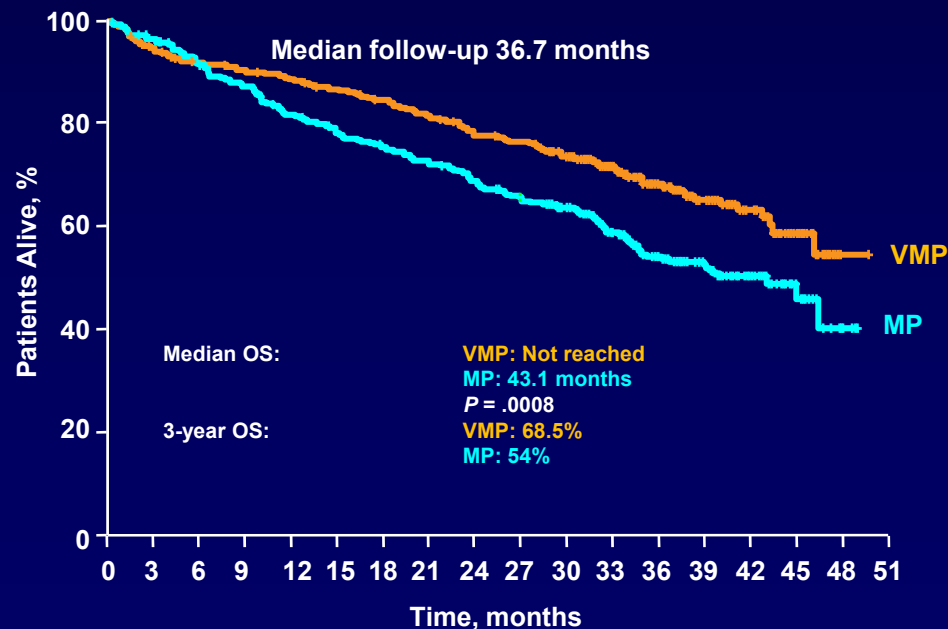


- 9 × 6-week cycles
- 54 weeks treatment
- Stratification for baseline β_2 -microglobulin and albumin levels and region
- Primary end point TTP

VISTA Trial: Response Rates, PFS, OS



Treatment	PFS, months	P value
MPV (n = 334)	24.0	< 0.001
MP (n = 338)	16.6	



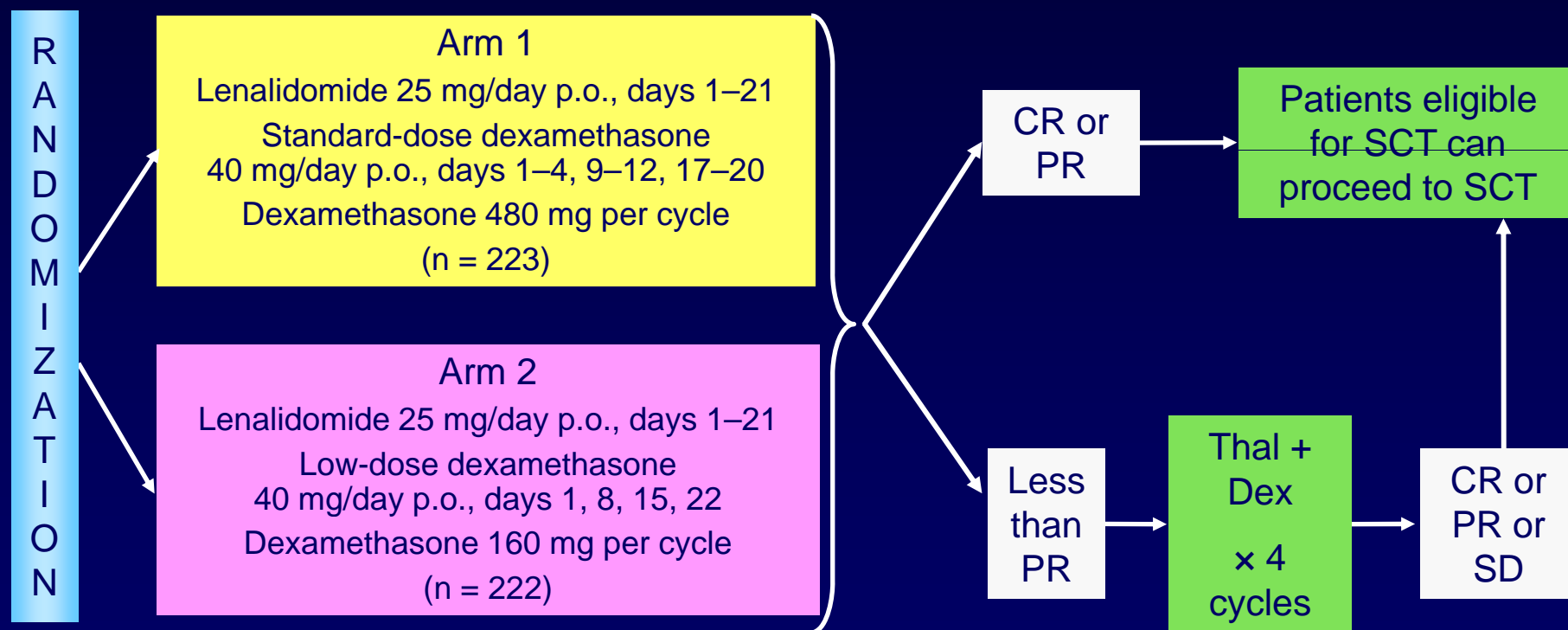
San Miguel J, et al. *N Engl J Med.* 2008;359(9):906-17.
 Mateos M-V, et al. *J Clin Oncol.* 2010;28(13):2259-2266.

VISTA Trial: Adverse Events

Adverse event	MPV, % (n = 340)	MP, % (n = 337)
Infection, grade 3 or 4	10	7
Neutropenia, grade 3 or 4	40	38
DVT, grade 3 or 4	1	1
Peripheral neuropathy		
Grade 3 or 4	13	0
Any grade	44	5
Death during treatment	5	4
Treatment-related death	1	2

ECOG-E4A03: Len + Standard or Low-Dose Dex in Newly Diagnosed MM (N = 445)

Four courses, every 28 days



ECOG-E4A03: 1-Year Survival Rate With Low-Dose vs High-Dose Dex by Age

	1-Year survival rate, %	<i>P</i> value
Age < 65 years		
Len + high-dose Dex	91	
Len + low-dose Dex	98	0.01
Age ≥ 65 years		
Len + high-dose Dex	83	
Len + low-dose Dex	94	0.004

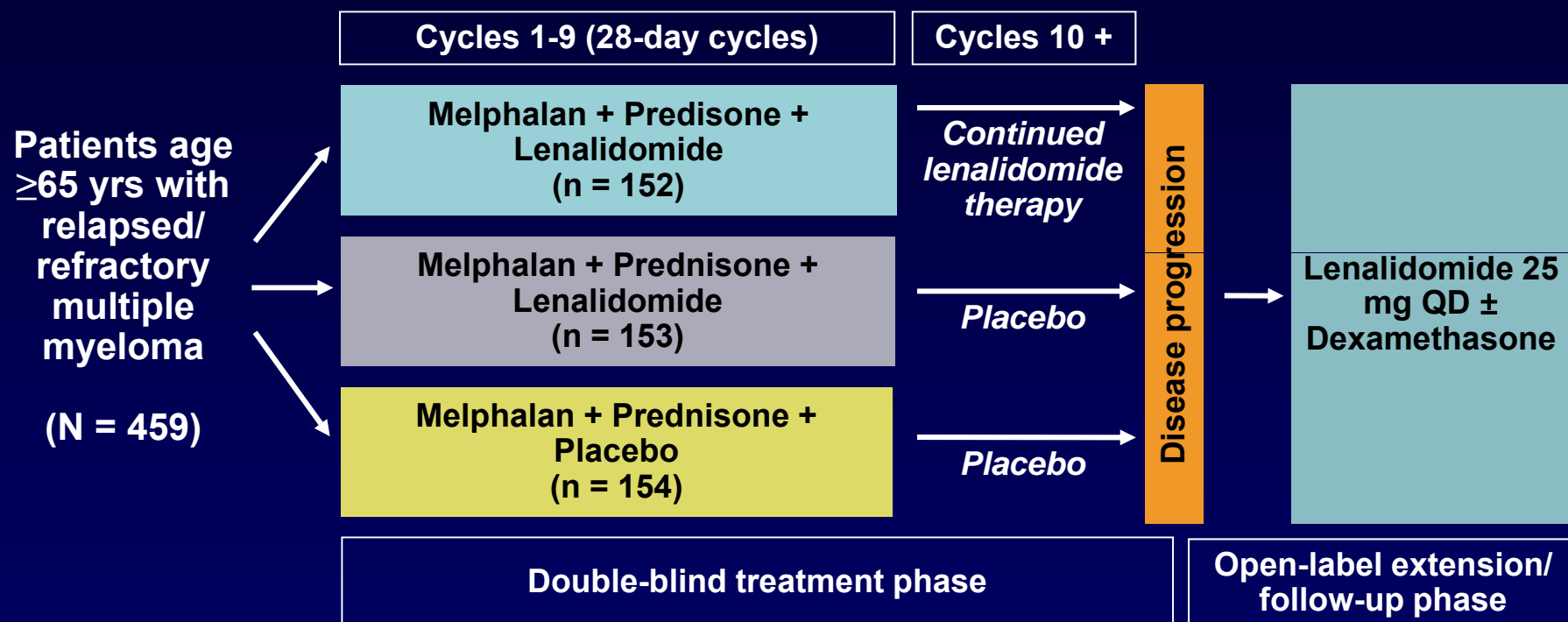
All patients in the high-dose Dex group were instructed to cross over to the low-dose group immediately

ECOG-E4A03: Adverse Events

Grade 3 or 4 Adverse Event	RD, % (n = 223)	Rd, % (n = 220)	P value
Infection or pneumonia	16	9	.04
DVT or PE	26	12	<.001
Neuropathy	2	2	.999
Cardiac ischemia	3	1	.068
Any nonhematologic AEs (grade ≥ 3)	65	48	<.001
AEs (grade ≥ 4)	21	14	<.001
Early deaths (<4 months)	5	1	.003

RD, lenalidomide/high-dose dexamethasone
Rd, lenalidomide/low-dose dexamethasone

Phase 3 Trial: MP ± Lenalidomide (R) in Newly Diagnosed Elderly Myeloma Pts



- Melphalan: 0.18 mg/kg on Days 1-4; Prednisone: 2 mg/kg on Days 1-4; Lenalidomide 10 mg QD PO on Days 1-21
- Patients stratified by age (≤ 75 yrs vs > 75 yrs and stage (ISS 1, 2 vs 3)
- Pilot study of 54 pts: RR = 81% (24% CR), TTP = 28 mos

MM-015: Best Response

Best overall response*	MPR-R (n = 152)	MPR (n = 153)	MP (n = 154)	P value (MPR-R vs MP)
ORR, %	77	67	49	< 0.001
CR‡	18	13	5	< 0.001
≥ VGPR§	32	33	11	< 0.001
PR	45	34	37	—
Median time to first response, months	1.9	1.9	2.8	< 0.001

* As measured using EBMT criteria.

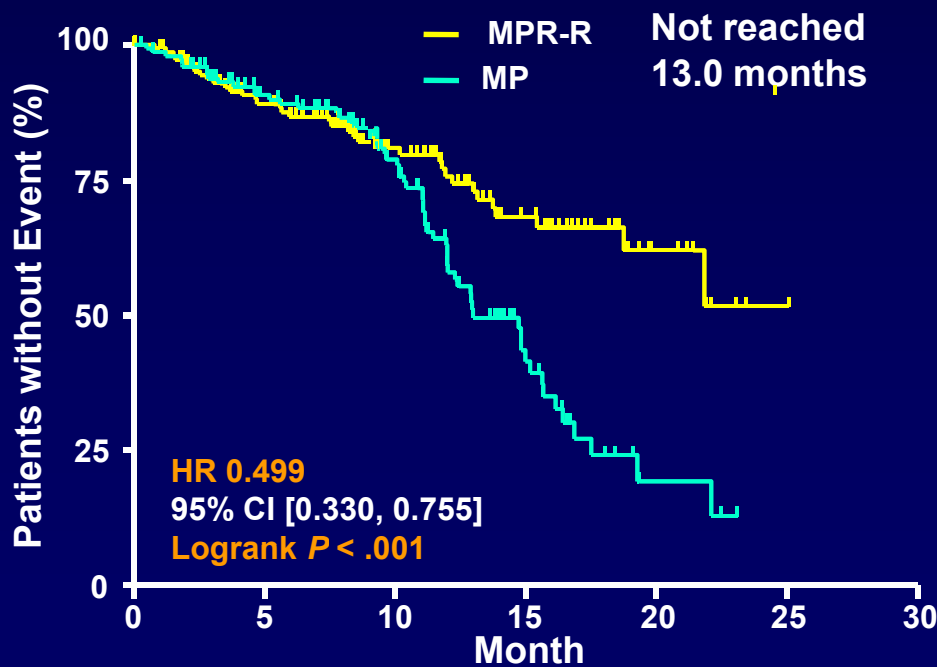
‡ Immunofixation-negative with or without bone marrow confirmation.

§ VGPR: > 90% reduction in M protein.

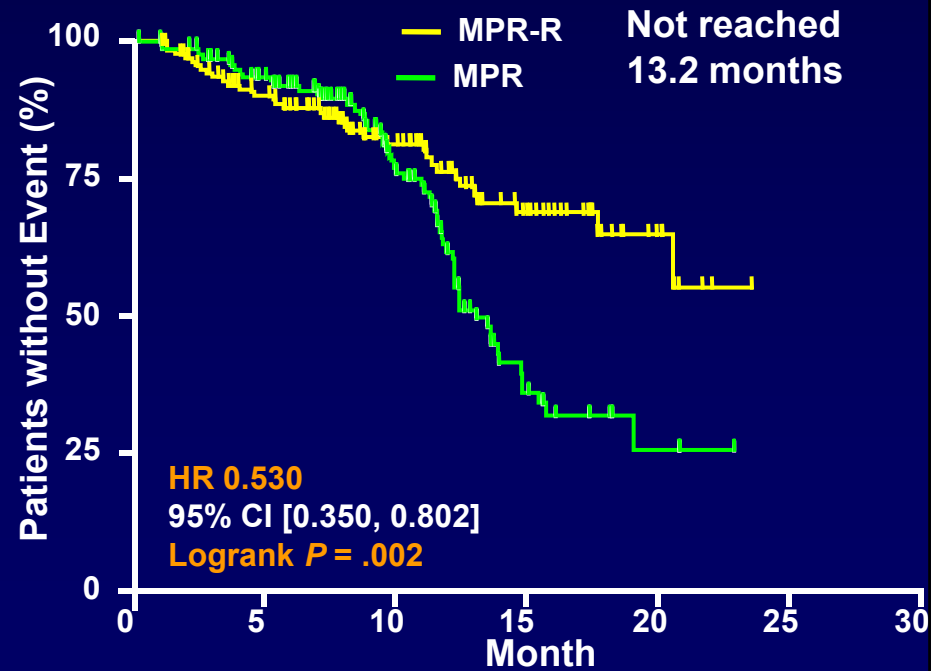
Response and PFS: MPR-R vs MPR vs MP

Response, %	MPR-R	MPR	MP
Overall response rate	77	67	49
Complete response	18	13	5

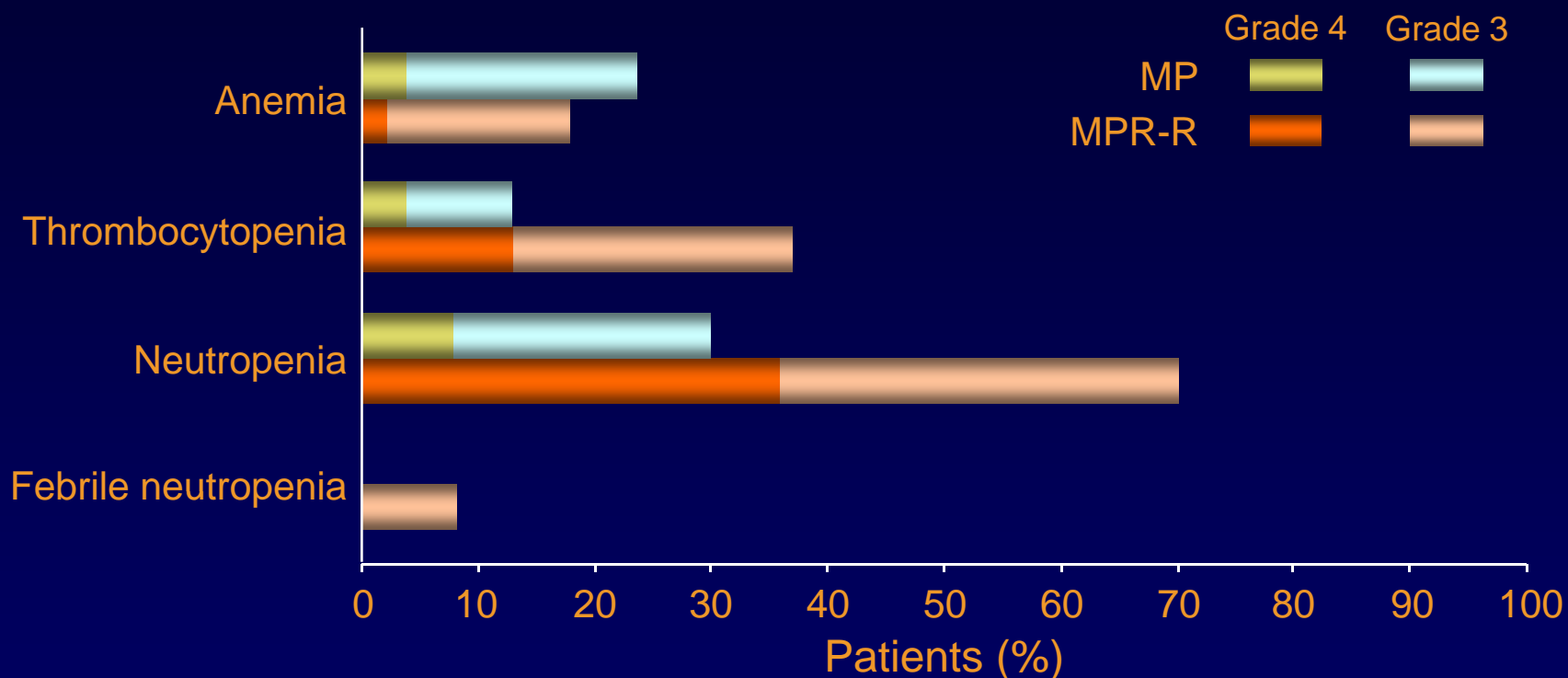
PFS: **MPR-R** vs **MP** (50% reduced risk)



PFS: **MPR-R** vs **MPR** (47% reduced risk)



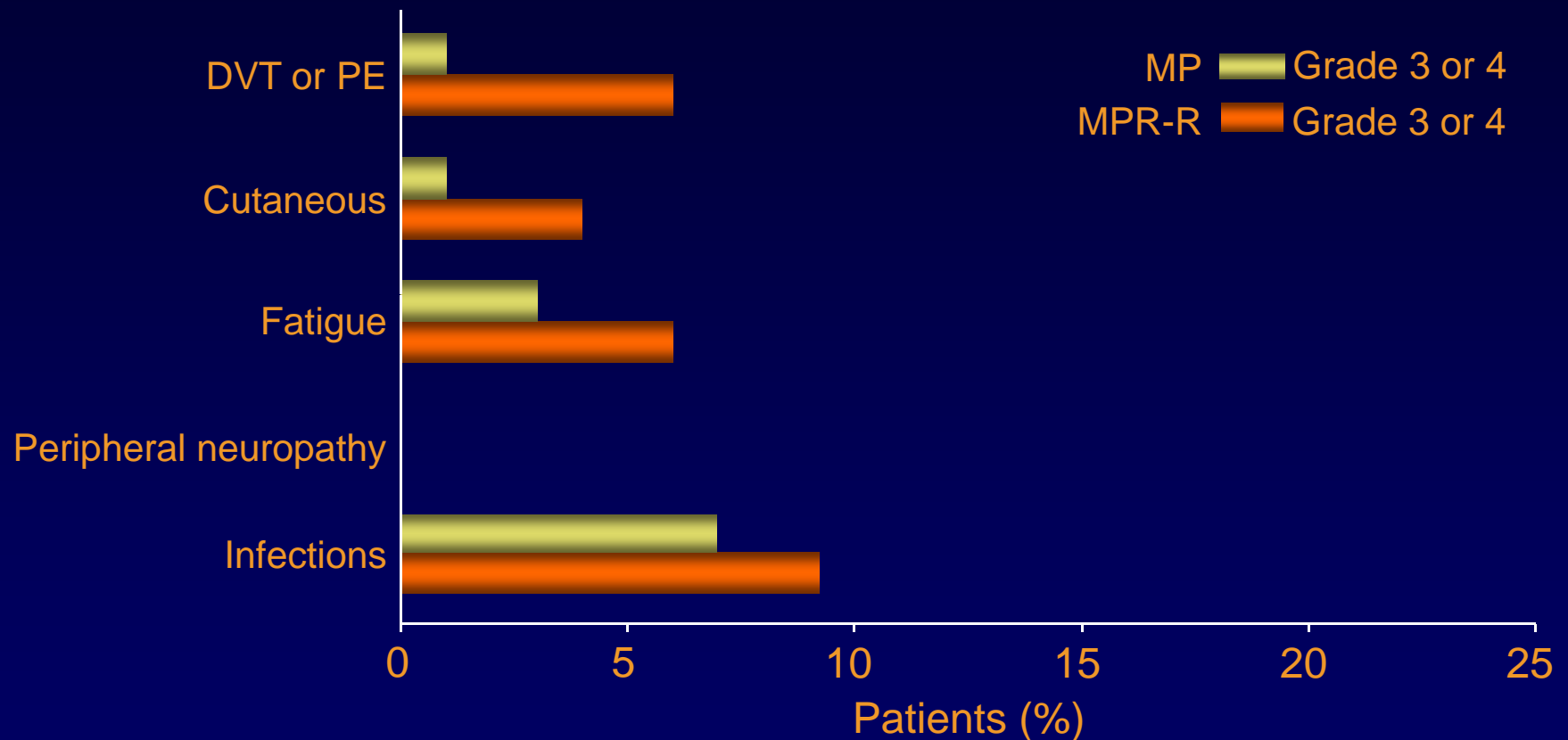
MM-015: Grade 3 or 4 Hematologic AEs



G-CSF administration: 49% (MPR-R) vs 29% (MP)

Platelet transfusion: 6% (MPR-R) vs 5% (MP)

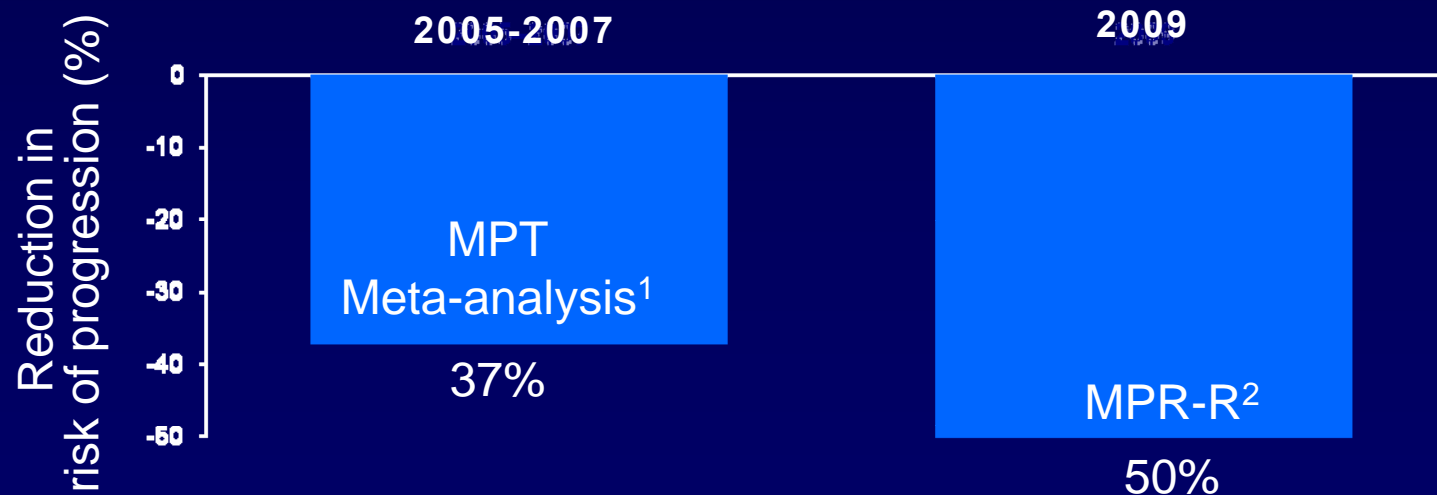
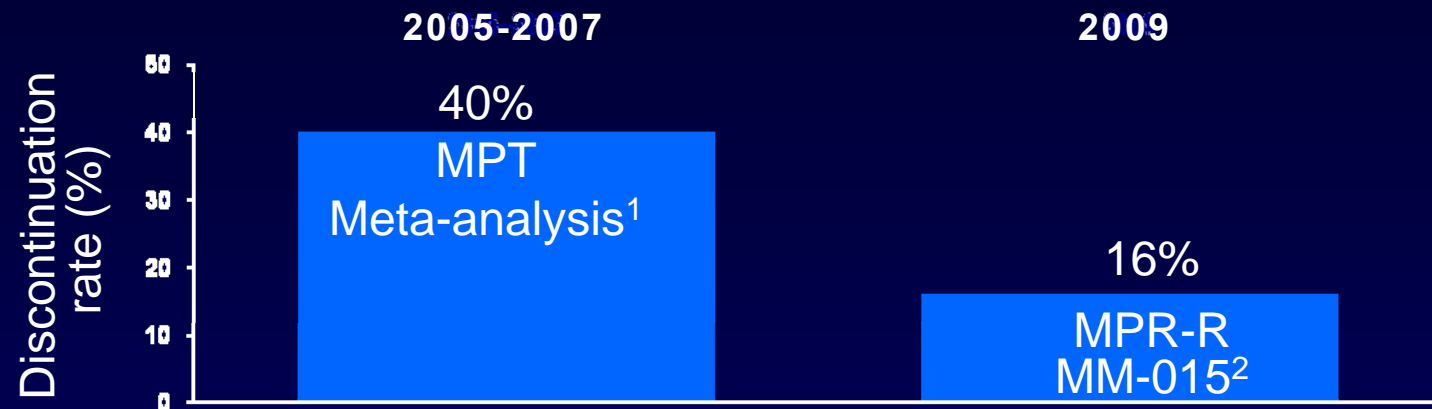
MM-015: Grade 3 or 4 Nonhematologic AEs



Overall rate of discontinuation due to AEs: 16% (MPR-R) vs 7% (MP)

Discontinuation due to hematologic AEs: 8% (MPR-R) vs 2% (MP)

MPR-R: Reduced Discontinuation and Progression Rates

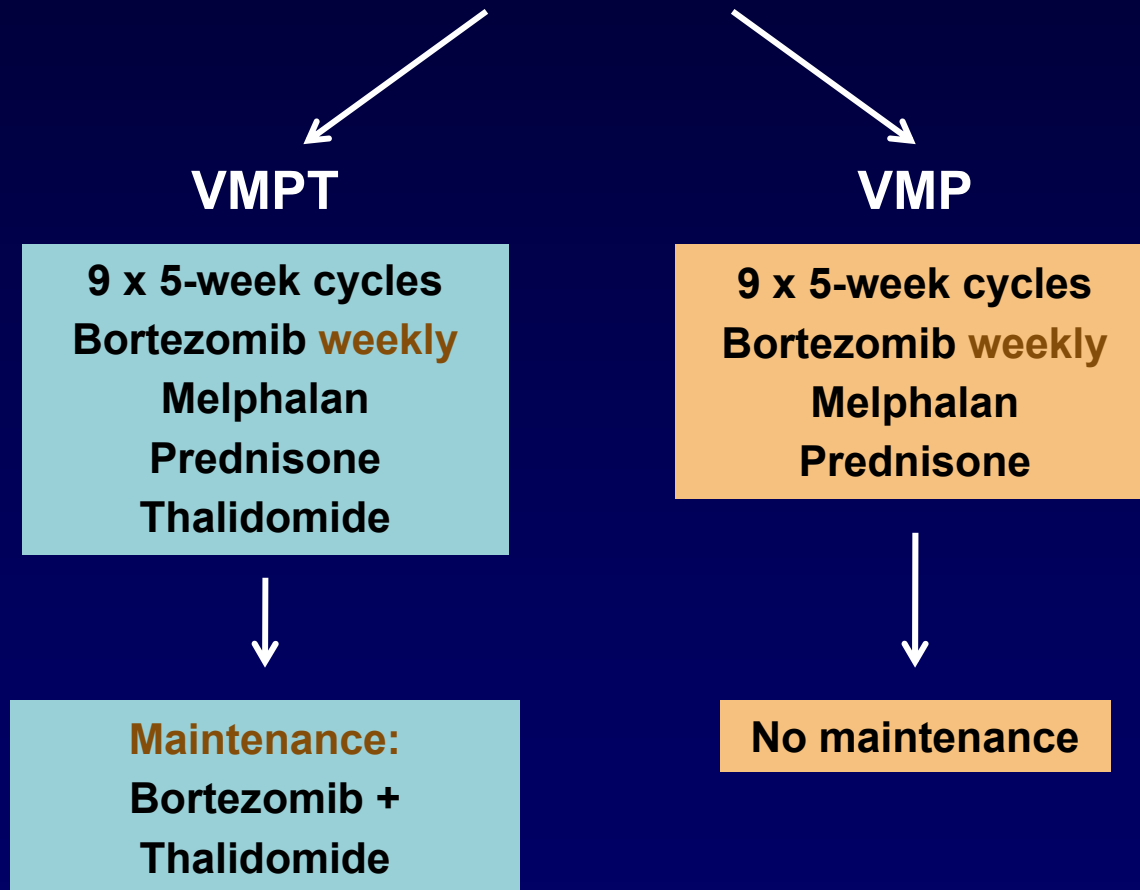


¹Kapoor P, et al. *Blood*. 2009;114: Abstract 615.

²Palumbo A, et al. *Blood*. 2009;114: Abstract 613.

Phase III: VMPT + VT vs VMP in Elderly Patients With Newly Diagnosed MM—GIMEMA Study

- Patients (N = 511): >65 years old; median age 71 years



Phase III: VMPT + VT vs VMP

VMPT + VT maintenance improves response rates and PFS

Median follow-up: 21.6 months

	VMPT + VT (n = 250)	VMP (n = 253)	P
CR	38%	24%	0.0008
≥VGPR	59%	50%	0.03
≥PR	89%	81%	0.01
3-year PFS	60%	42%	<0.007
3-year TTNT	75%	60%	0.0029
3-year OS	88.8%	89.2%	0.96

- Incidence of hematologic AEs generally similar between arms
 - Grade 3/4 neutropenia significantly more frequent with VMPT (38% vs 28.1%)
- Some nonhematologic AEs more common in VMPT vs VMP arm, including sensory neuropathy, infection
 - Grade 3/4 cardiologic AEs significantly more frequent with VMPT (10.4% vs 5.5%)

Phase III: VMPT + VT vs VMP

Comparison of efficacy and tolerability of different VMP schedules

	VISTA trial	GIMEMA trial: VMPT+VT vs VMP	
	VMP (twice weekly)	VMP (twice-weekly)	VMP (once weekly)
CR	30%	25%	23%
2-year PFS	48%	56%	58%
Sensory PN			
Any grade	44%	43%	21%
Grade 3/4	13%	14%	2%
Discontinuation due to PN	na	16%	4%
Total planned dose	67.6 mg/m ²	67.6 mg/m ²	46.8 mg/m ²
Total delivered dose	na	41 mg/m ²	40 mg/m ²

Weekly infusion of bortezomib decreases incidence of peripheral neuropathy

Phase III: VMP vs VTP in Newly Diagnosed Elderly Patients With MM

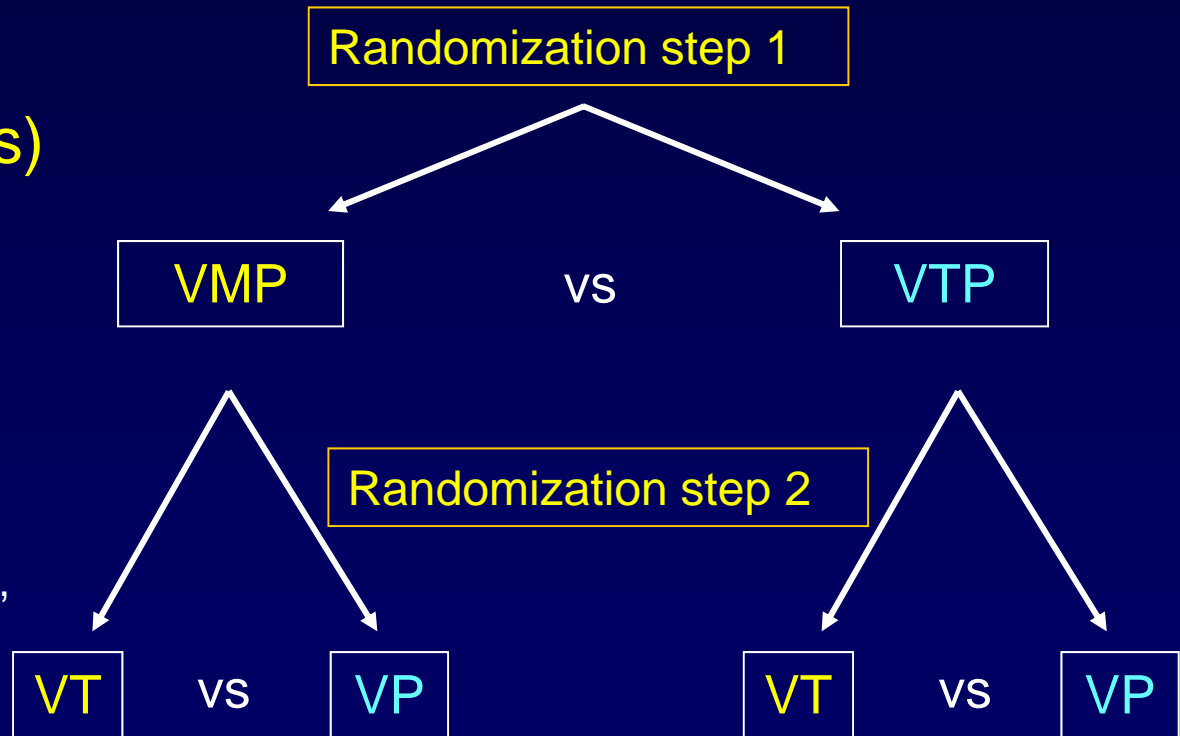
- **Patients** (n = 260), >65 years old (median age 73 years)
- **Multicenter, two-stage randomized trial**

Induction (max. 6 cycles)

- One 6-week cycle, bortezomib 2x weekly
- Five 5-week cycles, bortezomib 1x weekly

Maintenance (up to 3 years)

Bortezomib: 1.3 mg/m² (days 1, 4, 8, 11), every 3 months + thal:
50 mg daily or pred: 50 mg every 48 hours



Phase III: VMP vs VTP in Elderly Patients

Response to induction

	VMP (n = 130)	VTP (n = 130)
ORR	80%	81%
CR IF-	20%	27%
CR IF+	12%	10%
PR	48%	46%
Median time to first response	1.6 months	1.6 months
Median time to CR	4.4 months	4.9 months

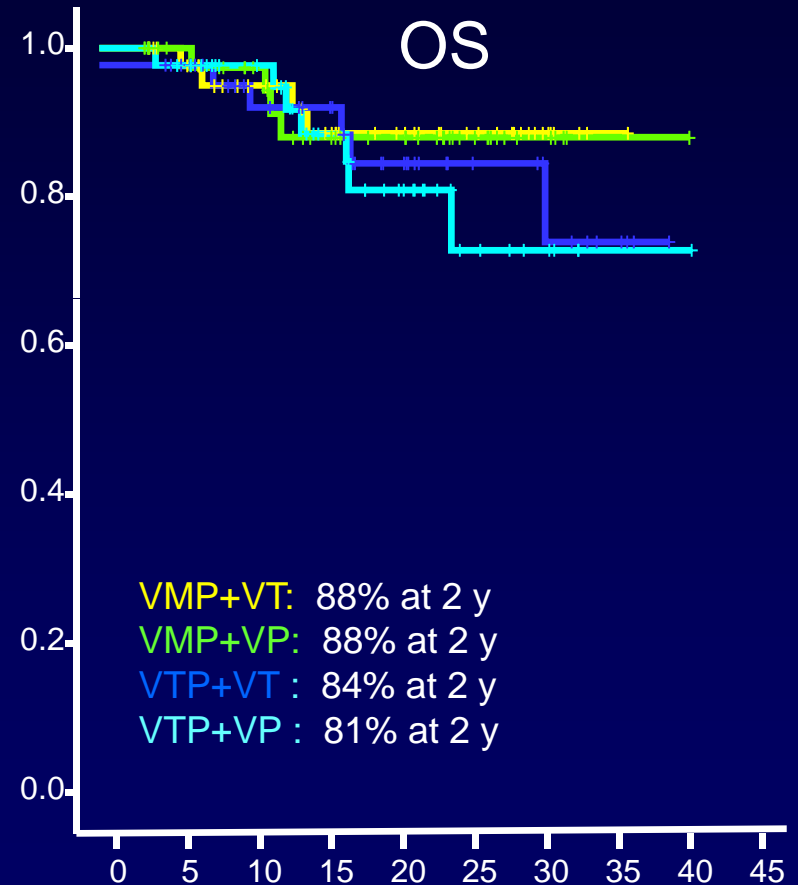
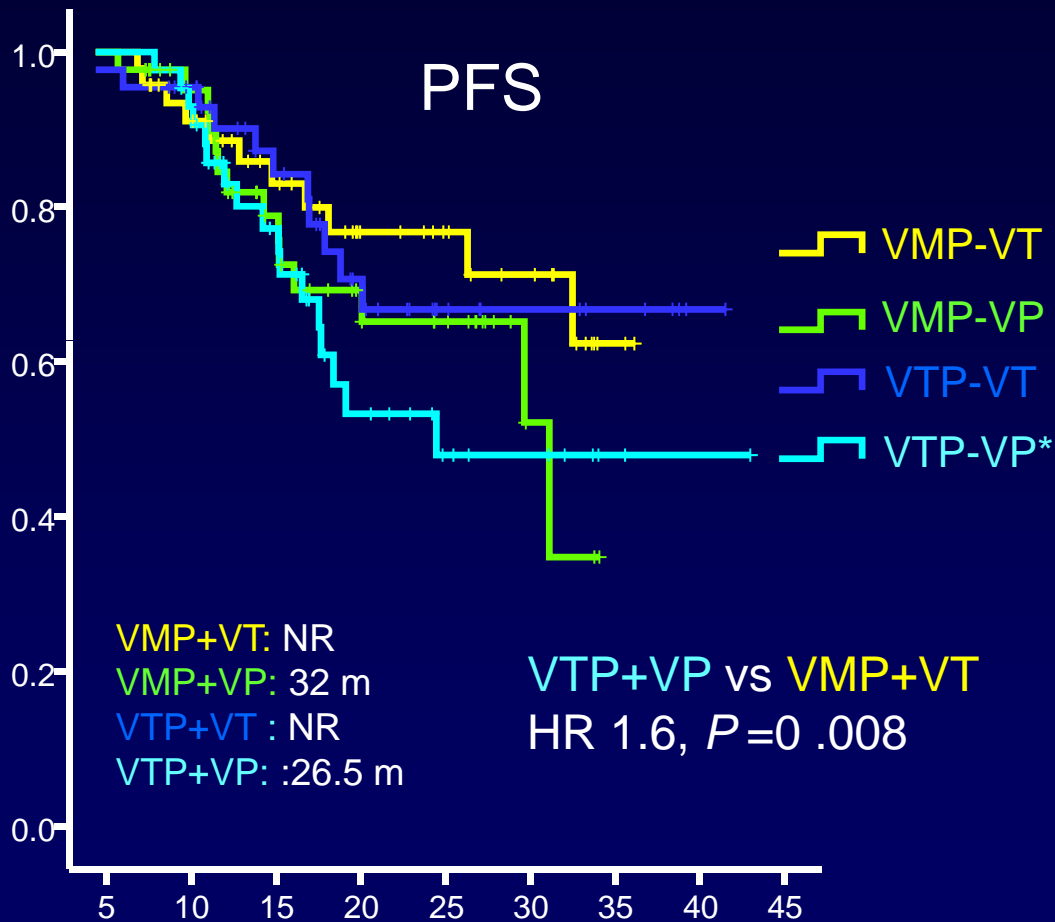
Response to maintenance therapy

	VT (n = 91)	VP (n = 87)
ORR	98%	99%
CR IF-	44%	39%
CR IF+	15%	16%
PR	39%	44%

Both maintenance regimens increased CR rate

Similar efficacy with VMP and VTP

Outcome of Different Cohorts (n = 178)



Cox regression analysis of PFS and OS with inverse probability weighting ($P=0.8$ for the interaction term)

**MYELOMA PATIENTS
WITH RENAL IMPAIRMENT**

Criteria for the Definition of Renal Response to Anti-Myeloma Therapy

Response	BASELINE eGFR* (mL/min/1.73 m ²)	Best CrCl RESPONSE
CRrenal	<50 mL/min	≥60 mL/min
PRrenal	<15 mL/min	30-59 mL/min
MRrenal	<15 mL/min 15-29 mL/min	15-29 mL/min 30-59 mL/min

*eGFR based on MDRD equation

Reversibility of Renal Failure in Newly Diagnosed Patients with MM and the Role of Novel Agents

- Patients (n = 82) with newly diagnosed MM and RI (=CrCl <50ml/min)

	Renal CR + PR
Group A (conventional chemotherapy + dex-based) (n = 28)	47%
Group B (IMiD-based) (n = 38)	51%
Group C (bortezomib-based) (n = 16)	82%

- Overall, 3/9 pts became dialysis-independent
- Multivariate analysis: bortezomib-based regimens significantly associated with higher renal response rate
- CrCl <30 ml/min associated with significantly lower probability of RCR or RPR in groups A and B ($P < 0.01$), but not in group C ($P = 0.529$)
- Median time to RPR
 - Similar in groups A and B (2.2 months Group A, 1.5 months Group B, $P = 0.587$), but significantly shorter for Group C (0.7 months, $P = 0.017$)
- Rapid improvement of renal function (≤ 1 month) associated with trend for longer survival

Renal Impairment Summary

IMWG Guidelines

In patients with renal impairment

- Available data support the safety and efficacy of bortezomib-based therapies in this setting and **thus bortezomib plus dexamethasone is the recommended treatment for myeloma patients with renal impairment of any grade.**
- Thalidomide is also an option for patients with severe renal impairment, although data are less extensive. A triple combination of bortezomib, thalidomide and dexamethasone may also be considered.
- Lenalidomide is a feasible and effective treatment option for patients with mild-to-moderate renal impairment, if it is used at the recommended reduced dose based on renal function.

Choice of Treatment for the Elderly Patients

“Aggressive” disease

MPV

“Nonaggressive” disease

MPT

Poor cytogenetics

MPV

Renal failure

Vel/Dex, MPV

History of peripheral neuropathy

Len-based

Very elderly-frail

MPT (Thal 100 mg/d)

**What Are Practical
Recommendations Regarding
Treatment Schedules?**

Recommendations for Adjusting Therapy

Autologous transplantation	Full dose chemotherapy	Reduced dose chemotherapy
<65 years	65–75 years	>75 years
<p>In good clinical condition, normal</p> <ul style="list-style-type: none"> • Cardiac • Pulmonary • Liver • Renal function 	<p>In good clinical condition, normal</p> <ul style="list-style-type: none"> • Cardiac • Pulmonary • Liver • Renal function <p><65 years</p> <p>With abnormal</p> <ul style="list-style-type: none"> • Cardiac • Pulmonary • Liver • Renal function 	<p>In good clinical condition, normal</p> <ul style="list-style-type: none"> • Cardiac • Pulmonary • Liver • Renal function <p>65–75 years</p> <p>With abnormal</p> <ul style="list-style-type: none"> • Cardiac • Pulmonary • Liver • Renal function

Recommended Dose Reductions for Thalidomide-Based Combinations

	65–75 years	>75 years	Further dose reduction
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

Recommended Dose Adjustments for Bortezomib-Based Combinations

Depending on age and comorbidities (heart, lung, kidney, liver)

	<65 years	65–75 years	>75 years
Bortezomib	1.3 mg/m ² twice weekly	1.3 mg/m ² One cycle: twice weekly Then: once weekly	1.3 mg/m ² once weekly

If a Grade 3/4 AE occurs:

1. Discontinue therapy
2. Wait for toxicity to resolve to Grade 1
3. Restart at a lower dose

What Would I Recommend at First Relapse?

Main Randomized Trials of Treatment of Relapsed/Refractory Myeloma

Regimen	ORR, %	CR, %	TTP, mo	OS
Bort vs Dex ¹	38 vs 18	6 vs 1	6.2 vs 3.5	80% vs 66% at 1 year
Bort + Doxil vs Bort ²	44 vs 41	4 vs 2	9.3 vs 6.5	76% vs 65% at 15 months
Len/Dex vs Dex ³	61 vs 19.9	14.1 vs 0.6	11.1 vs 4.7	29.6 vs 20.2 months
Len/Dex vs Dex ⁴	60.2 vs 24	15.9 vs 3.4	11.3 vs 4.7	Not reached vs 20.6 months

1. Richardson PG, et al. *N Engl J Med.* 2005;352(24):2487-2498.
2. Orloski RZ, et al. *J Clin Oncol.* 2007;25(25):3892-3901.
3. Weber DM, et al. *N Engl J Med.* 2007;357(21):2133-2142.
4. Dimopoulos M, et al. *N Engl J Med.* 2007;357(21):2123-2132.

Conclusions

- **MPT and MPV**: the standard of care for patients who are not eligible for a transplantation
- **MPR + R**: a possible new standard of care
- Special attention for “frail” population

- Balance between efficacy and safety
- Peripheral neuropathy for bortezomib- and thalidomide- based therapies
- Fatigue and hematologic toxicity for lenalidomide-based regimens