

Initial Treatment of an Elderly Patient with Multiple Myeloma

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Disclosures for Thierry Facon, MD

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Janssen-Cilag

What Therapy Would You Recommend at This Time?

- **MPT (melphalan, prednisone, thalidomide)**
- **MPV (melphalan, prednisone, bortezomib)**
- **Lenalidomide and dexamethasone**
- **MPR (melphalan, prednisone, lenalidomide)**
- **Bortezomib as a single agent**
- **Bortezomib with dexamethasone**
- **VAD (vincristine, doxorubicin, dexamethasone)**
- **CA (cyclophosphamide + doxorubicin)**
- **Thalidomide and dexamethasone**

Reasonable, EMEA-Approved Choices

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MP vs MPT Studies: Patient Characteristics and MPT Regimens

	GIMEMA ^{1,2}	IFM 99-06 ³	IFM 01-01 ⁴	NMSG ⁵	HOVON ⁶
No.pts (MPT)	331 (167)	447 (125)	232 (113)	363 (182)	333 (165)
Age					
Median	72	69	78.5	74.5 (mean)	72
Range	60-85	65-75	75-89	49-92	NA
WHO 3/4,%	5	8	7	30	4
MPT regimen					
No. cycles	6	12	12	Until plateau	Until plateau
M dosing	4 mg/m ² d1-7	0.25 mg/kg d1-4	0.2 mg/kg d1-4	0.25 mg/kg d1-4	0.25 mg/kg d1-5
Thal. dosing	100	up to 400	100	up to 400	200
Maintenance	+	-	-	+	+

1. Palumbo A, et al. *Lancet*. 2006;367(9513):825-831.

2. Palumbo A, et al. *Blood*. 2008;112(8):3107-3114.

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

4. Hulin C, et al. *J Clin Oncol*. 2009;27(22):3664-3670.

5. Waage A, et al. *Blood*. 2007;110: Abstract 78.

6. Wijermans P, et al. *Blood*. 2008;112: Abstract 649.

MP vs MPT: PFS and OS

GIMEMA^{1,2} IFM 99-06³ IFM 01-01⁴ NMSG⁵ HOVON⁶

PFS (med, mo.)

MP	14.5	18	18.5	14	10*
MPT	21.8	27.5	24	16	13
P	.0004	<.0001	.001	TTP Sig.	<.001

OS (med,mo.)

MP	47.6	33	29	33	30
MPT	45.0	51.5	44	29	37
P	NS	.0006	.028	NS	NS

* Event-free survival

- In 5/5 studies, MPT was superior to MP in terms of PFS and/or TTP
- In 2/5 studies, MPT was superior to MP in terms of OS

1. Palumbo A, et al. *Lancet*. 2006;367(9513):825-831.

2. Palumbo A, et al. *Blood*. 2008;112(8):3107-3114.

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

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Other Reasonable Choice:CTD

MRC Myeloma IX

Nonintensive Pathway

Older, less fit patients (age > 65 years)

RANDOMIZATION

Clodronate	VS	Zoledronic acid
MP	VS	CTDa

RANDOMIZATION

Thalidomide	VS	No thalidomide
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Response	Patients, %	
	CTDa	MP
CR	22.5	6
≥VGPR	47.5	9.5
≥PR	82.5	48.7

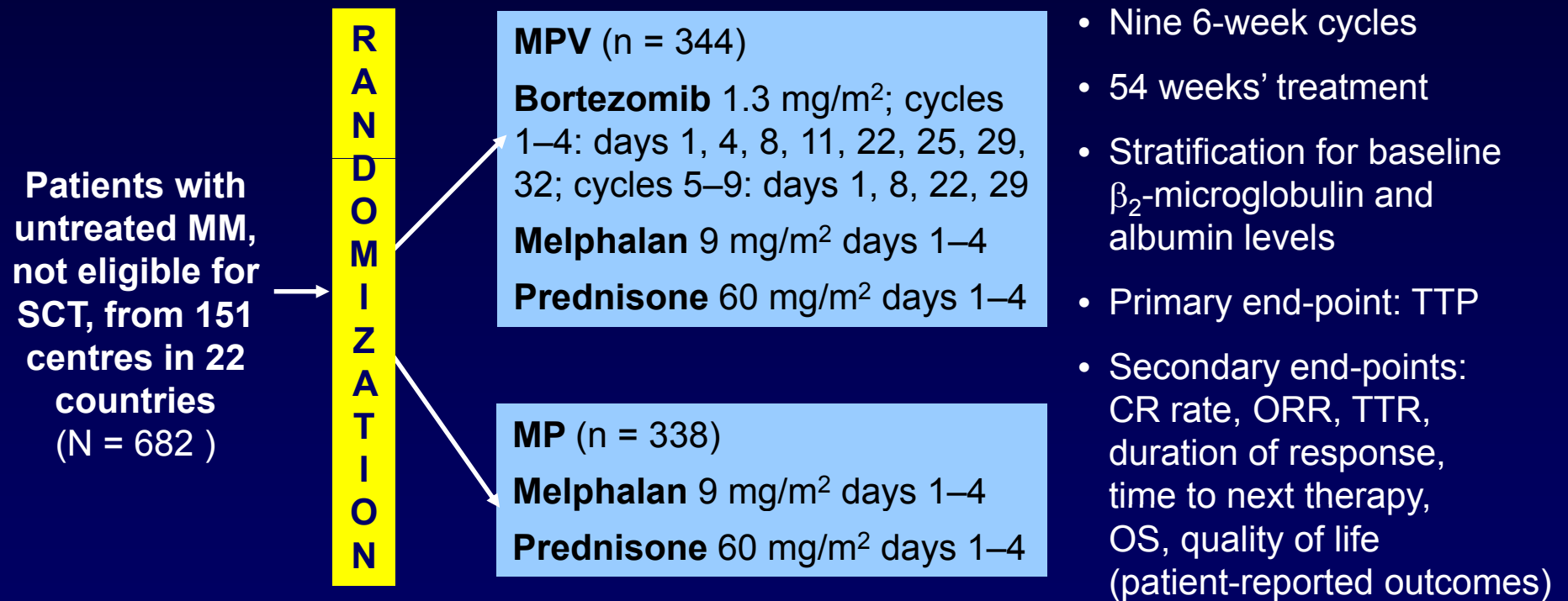
CTDa: cyclophosphamide 500 mg orally, once weekly; thalidomide 200 mg/day; dexamethasone 20 mg, days 1–4 and 15–18 of a 28-day cycle

CTDa = cyclophosphamide, thalidomide, dexamethasone.

Morgan GJ, et al. *Blood*. 2007;110: Abstract 3593.

Owen RG, et al. Presentation at: International Myeloma Workshop; February 26 – March 1, 2009; Washington, DC: Abstract 547.

MPV versus MP in Previously Untreated MM : VISTA Study



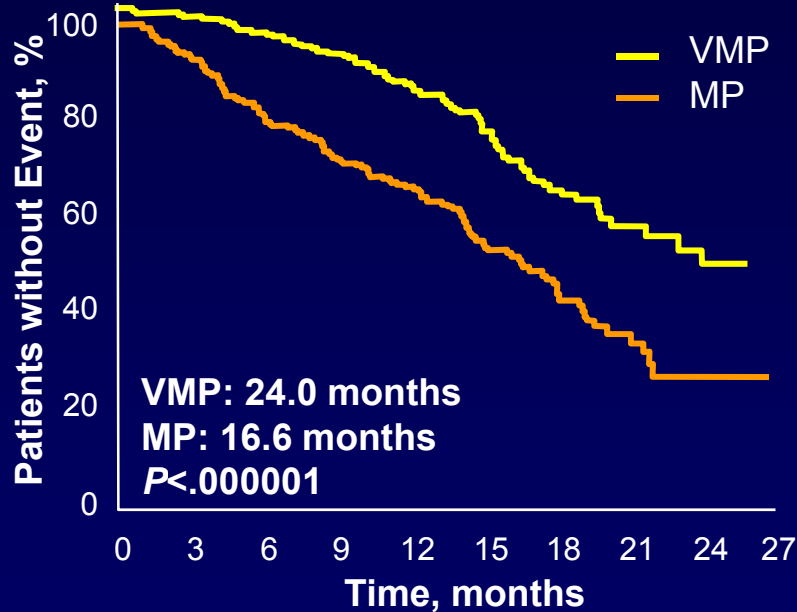
VISTA: Efficacy Data

ORR: VMP 71%, MP 35%

CR: VMP 30%, MP 4%

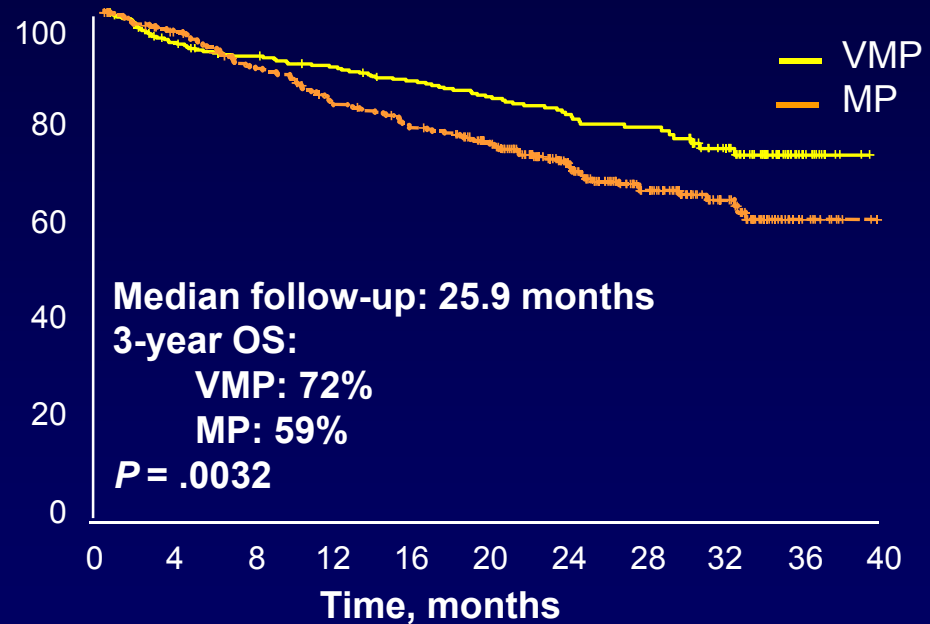
Time to Progression

~ 52% reduced risk of progression on VMP



Overall Survival

~ 36% reduced risk of death on VMP

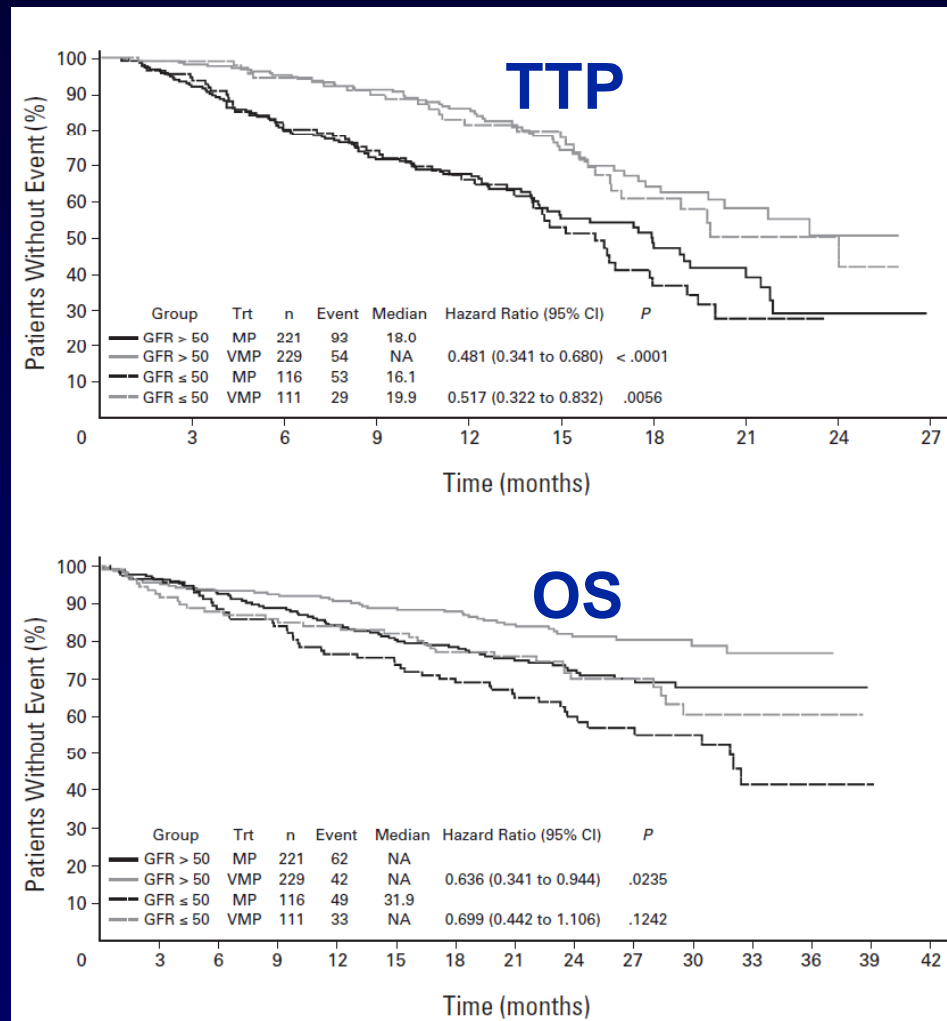


- Only 5% “true” nonresponders
Treatment-related death: 2% in both arms

VISTA: VMP Is Effective in Patients With Renal Impairment

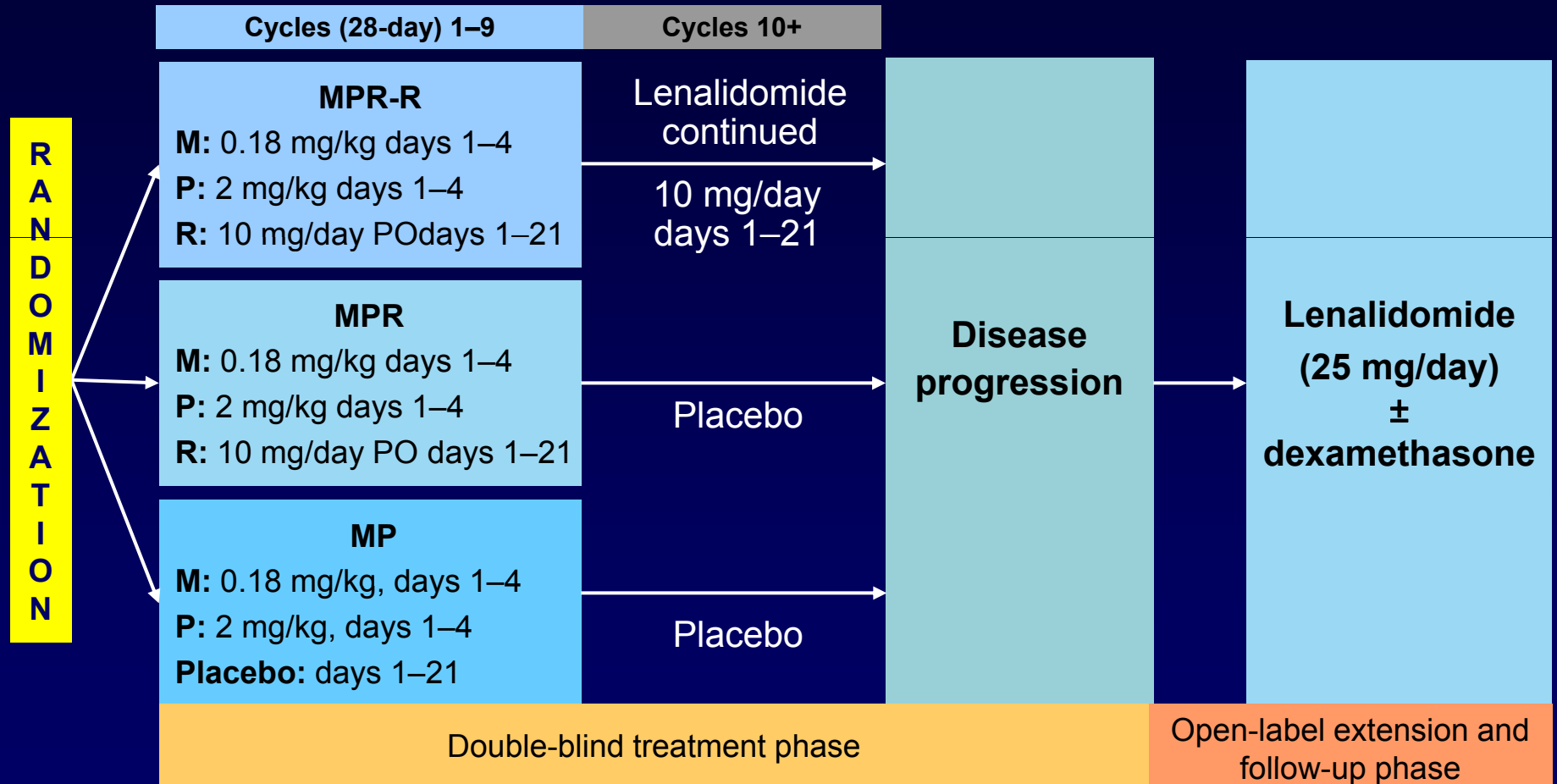
- **VMP more effective than MP in patients with renal impairment as indicated by ORR, CR rate, time to first response, duration of response, TTP**
- **Reversal of renal impairment (= improvement in GFR from <50 mL/min at baseline to >60 mL/min on treatment)**

VMP: 44% vs MP: 34%



MM-015: Phase III Trial of MPR vs MP in Newly Diagnosed MM

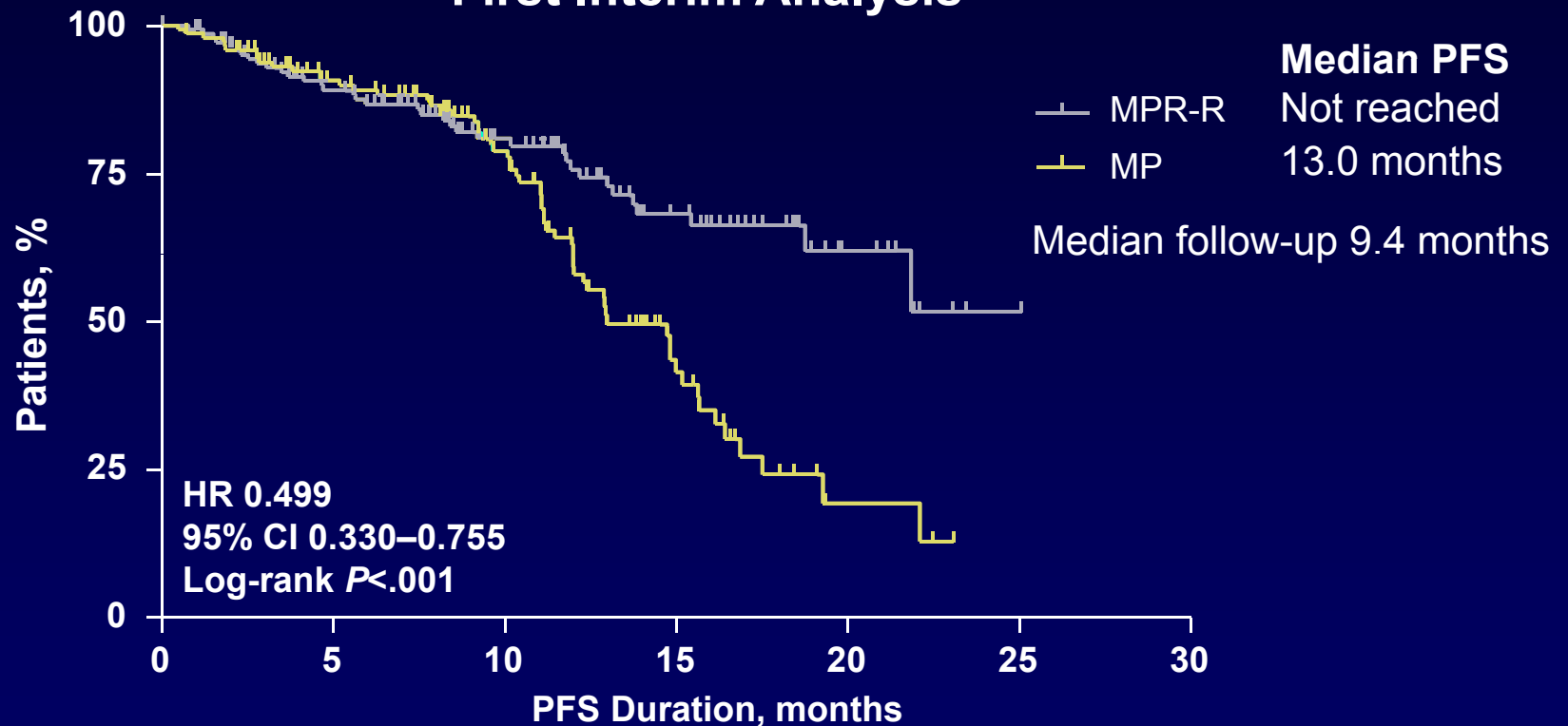
51 centres in Europe, Australia, and Israel (N = 459)



Stratification by age (≤ 75 vs > 75 years) and ISS stage (1, 2, or 3)

MM-015: MPR-R vs MP / PFS

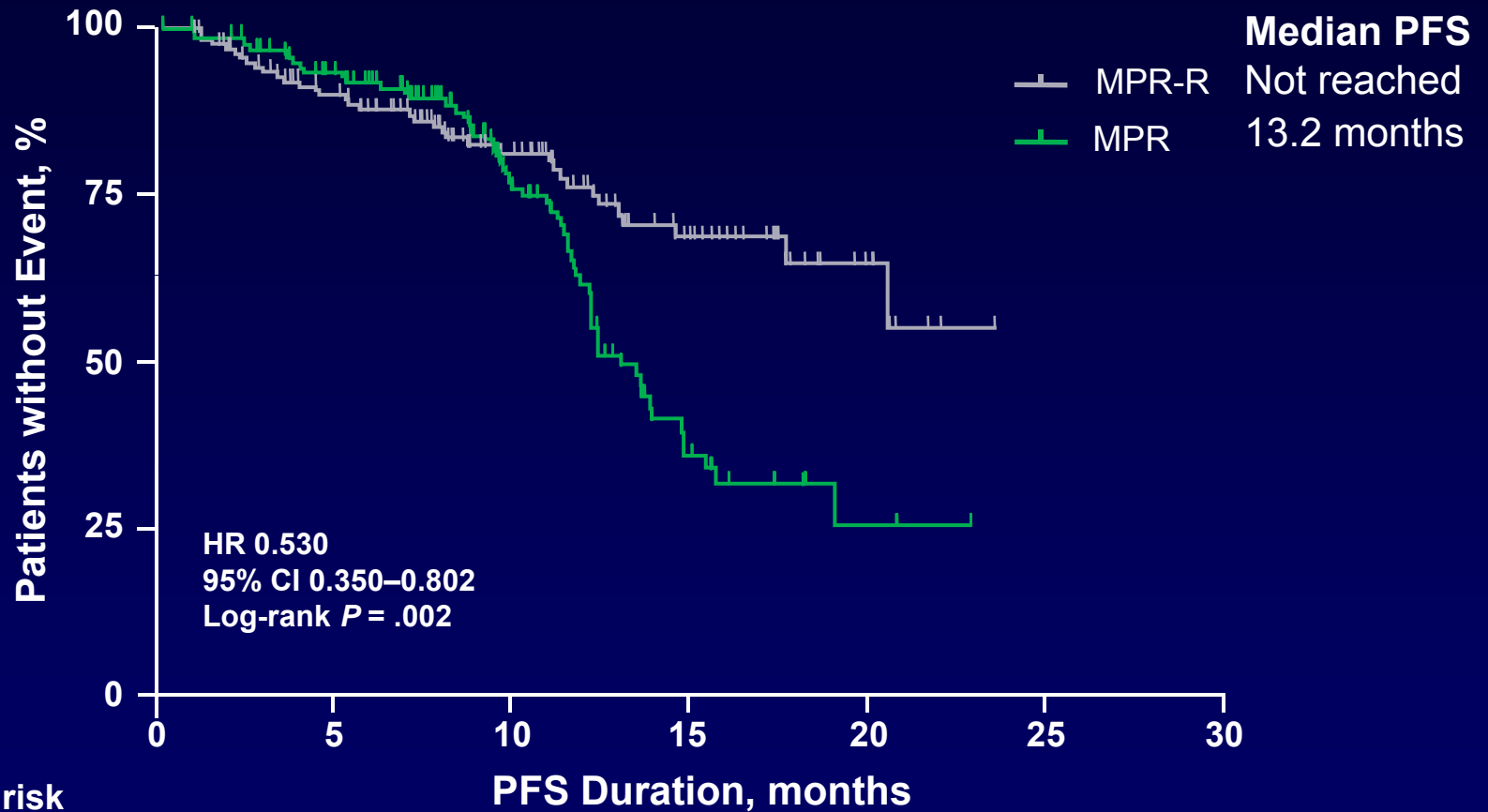
First Interim Analysis



No at risk

MPR-R	152	115	70	36	11	2	1
MP	154	114	77	21	4	1	1

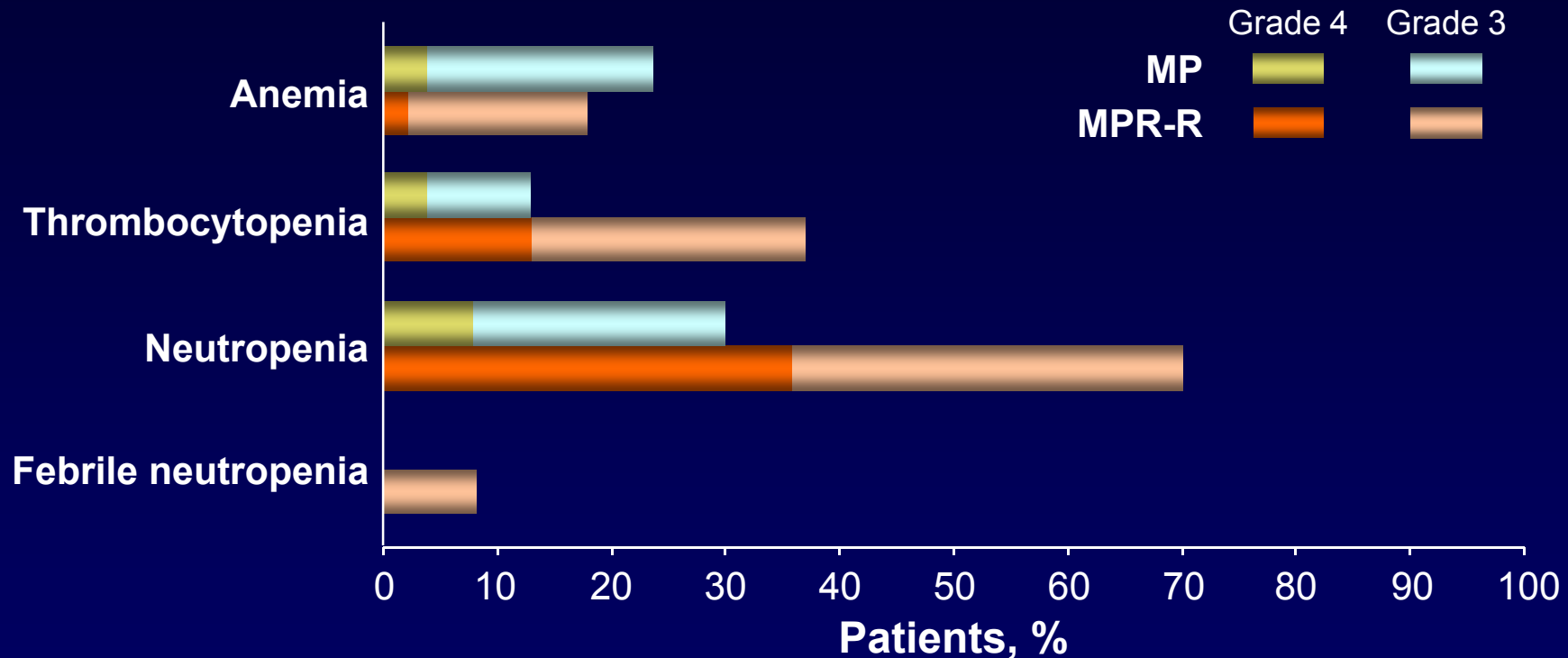
MM-015: MPR-R vs MPR / PFS



No at risk

	0	5	10	15	20	25	30
MPR-R	152	115	70	36	11	2	1
MPR	153	122	78	20	5	1	1

MM-015: Grade 3 or 4 Hematologic Adverse Events



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

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

“MPR + R : Too Early to Make a Recommendation!”

- **MM-015 study results are preliminary (interim analysis with median follow-up of 9 months, no survival results). Results from other MPR studies awaited (HOVON 87)**
- **In MM-015, maintenance lenalidomide results promising but further analysis needed to understand MPR induction results**
- **This combination is not yet approved**

Other (Very) Reasonable Choices Clinical Trials

- **Rd vs MPT (IFM2007/01-MM-020-FIRST)**
- **MPR vs MPT (HOVON 87)**
- **CRD vs CTD (MRC Myeloma XI)**

FIRST: Phase III Trial of Len + Low-Dose Dex versus MPT (IFM 07-01; MM-020)

Inclusion criteria

- Previously untreated MM
- Age ≥ 65 years or not eligible for a transplant
- No neuropathy of grade >2

N = 1590

Centres in EU, Switzerland, USA, and Canada

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Lenalidomide 25 mg/day, days 1–21 of every 28-day cycle
Dexamethasone* 40 mg/day, days 1, 8, 15, 22 of every 28-day cycle

Until disease progression

Lenalidomide 25 mg/day, days 1–21 of every 28-day cycle
Dexamethasone* 40 mg/day, days 1, 8, 15, 22 of every 28-day cycle

Eighteen 4-week cycles

Melphalan* 0.25 mg/kg/day, days 1–4 of every 42-day cycle
Prednisone 2.0 mg/kg/day, days 1–4 of every 42-day cycle
Thalidomide* 200 mg/day, daily through every 42-day cycle

Twelve 6-week cycles

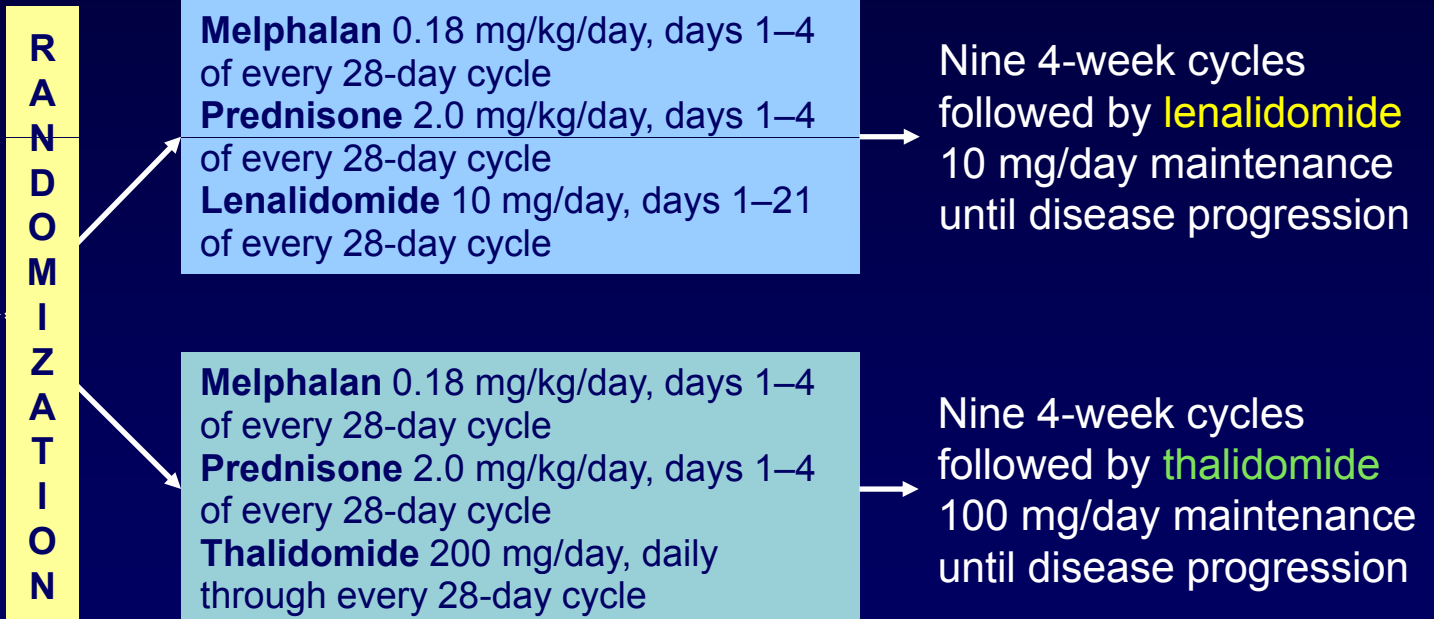
*In patients aged > 75 years: Dex 20 mg/day, melphalan 0.20 mg/kg/day, thalidomide 100 mg/day

Primary endpoint: PFS

HOVON-87: MPT versus MPR in Transplant-Ineligible Patients with Newly Diagnosed MM

Inclusion criteria

- Previously untreated MM
- Age ≥ 65 years or not eligible for a transplant
- WPSS score 0–3 in patients aged <75 years; 0–2 in patients aged ≥ 75 years



Primary endpoint: PFS

What Could Be the Options in the Future?

- **Defined duration of therapy + TFI:**
 - MPT or VMP
- **Continuous Treatment model**
 - Short initial treatment + maintenance treatment: VMP+VT, MPR+R or MP+?+R
 - Same combination until PD: Rd

What Would You Recommend Now?

- **Continue MPT at same dose**
- **Continue with lenalidomide 25 mg as maintenance**
- **Continue with thalidomide maintenance**
- **Observe off therapy**

What Would You Recommend Now?

- **Continue MPT at same dose**

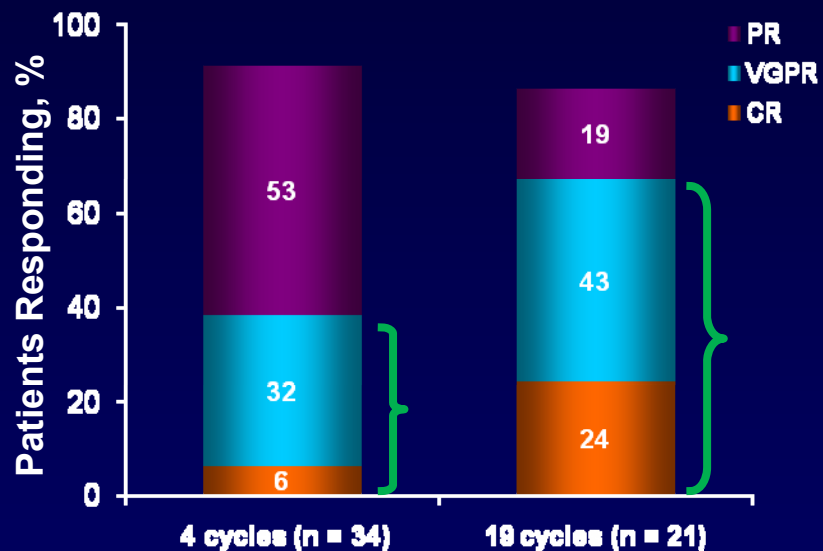
In this patient, because 4 cycles is too short

- **Continue with lenalidomide 25 mg as maintenance**
- **Continue with thalidomide maintenance**
- **Observe off therapy**

Maintenance is NOT routine practice at the present time!

Longer-Term Results with Lenalidomide + Dexamethasone

Mayo Phase II¹



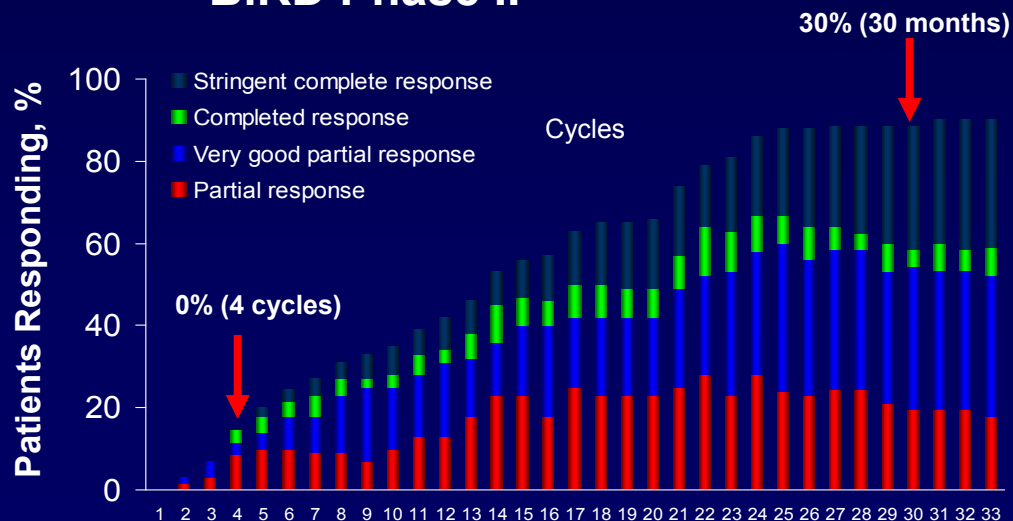
38% → **67%**
VGPR or better

Stringent CR (sCR)

0% (4 cycles) → 30% (30 months)

OS 93% at 4 years

BiRD Phase II²



1. Lacy MQ, et al. *Mayo Clin Proc.* 2007;82(10):1179-1184.
 2. Niesvizky R, et al. *Blood.* 2008;111:1101-1109.

MM-015: Grade 3 or 4 Adverse Events After Cycle 9 (Continuous Lenalidomide)

	MPR-R (N = 75)	MP (N = 94)
Anemia	0%	5%
Thrombocytopenia	3%	1%
Neutropenia	1%	0%
DVT	3%	0%
Rash	0%	0%
Fatigue	1%	0%
Peripheral neuropathy	0%	0%

What Would You Recommend at First Relapse?

- **Restart MPT**
- **MPR**
- **Bortezomib alone**
- **Bortezomib and dexamethasone**
- **Lenalidomide alone**
- **Lenalidomide and dexamethasone**
- **VAD**

Treatment at Relapse

