Should All Transplant-Ineligible Patients Receive a Melphalan-Based Induction Regimen?

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EMORY UNIVERSITY WINSHIP CANCER INSTITUTE

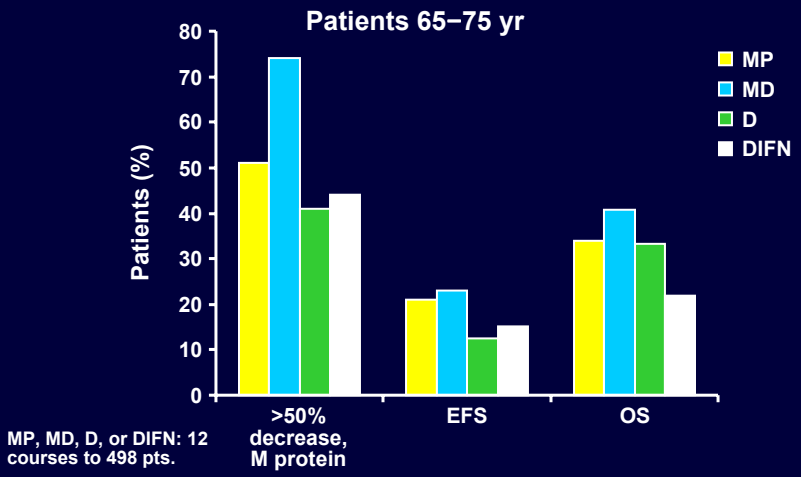
Why Approach Older Patients Differently?

- More sensitive to toxicity
- Less physical reserve
- Considerations are either Dex or Melphalan Based therapy

Effective therapy should:

- Induce high response rates
- Not have severe toxicity
- Should improve survival compared to standard comparator

What Is the Role of Dexamethasone in Older Patients?



MP, MD, D, or DIFN: 12 courses to 498 pts.

FU, 82.8 mo.
OS, 35.0 mo.
EFS, 18.3 mo.

Facon T et al. *Blood*. 2006;1292.

Thalidomide/Dexamethasone vs MP in Elderly MM Patients

Patients with untreated MM
Median age, 72 yr
N=289

Thalidomide 50–400 mg/d
Dexamethasone 40 mg
d1–4 all cycles; d1–4,15–18 odd cycles q4wk
N=145

Melphalan 0.25 mg/kg, d1–4
Prednisolone 2 mg/kg, d1–4
q4wk–q6wk
N=143

≥SD

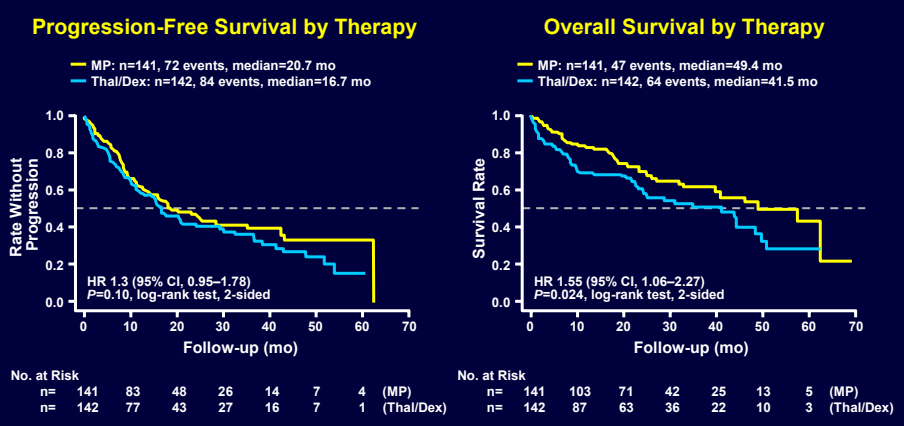
Thalidomide ≤100 mg/d
IFNα-2b (3 MIU, t.i.w)
N=54

IFNα-2b
3 MIU, t.i.w.
N=57

All patients received zoledronate 4 mg q4wk
Primary end points: PFS, EFS, toxicity
Secondary end points: RR, time to response, OS

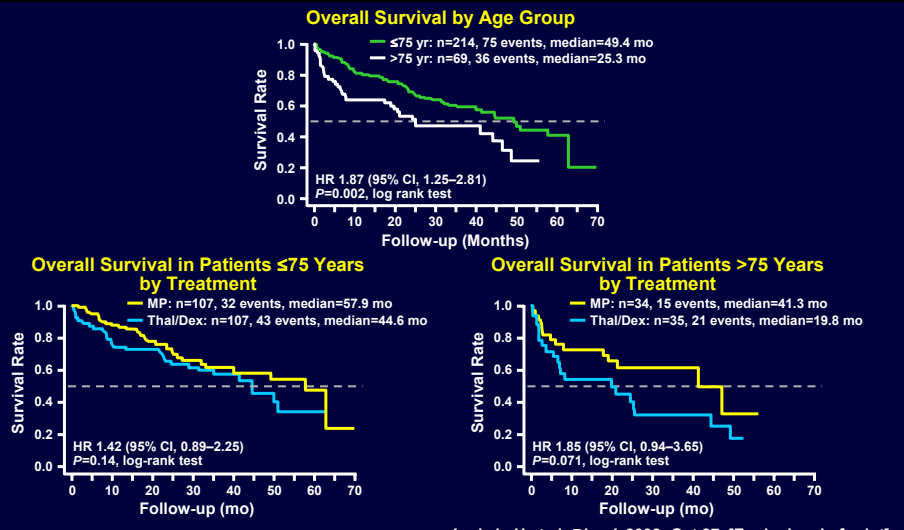
Ludwig H et al. *Blood*. 2008; Oct 27. [Epub ahead of print].

Use of TD Is Inferior to MP for Older Patients



Ludwig H et al. *Blood*. 2008; Oct 27. [Epub ahead of print].

Effect of Age on Survival



Ludwig H et al. *Blood*. 2008; Oct 27. [Epub ahead of print].

MP vs MP + Thalidomide (MPT) in Elderly Patients With Multiple Myeloma

GIMEMA Phase 3 Randomized Controlled Trial

Newly diagnosed MM patients

Age >65 yr

(median, 72 yr)

N=255

MPT Arm
Melphalan, 4 mg/m^2 (7 days per month)
Prednisone, 40 mg/m^2 (7 days per month)
Thalidomide, 100 mg/d (continuously)*
(n=129)

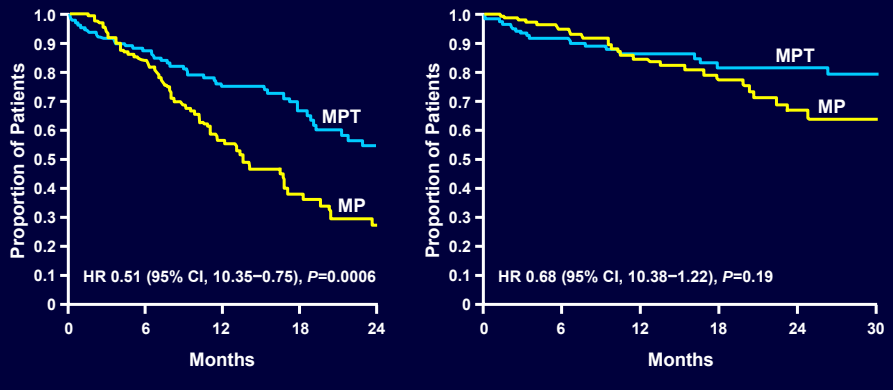
→ ×**6 courses**

MP Arm
Melphalan, 4 mg/m^2 (7 days per month)
Prednisone, 40 mg/m^2 (7 days per month)
(n=126)

* Thalidomide dose reduced to 50% if grade 2 toxicity.
Enoxaparin prophylaxis added to protocol in December 2003.

Palumbo A et al. *Lancet*. 2006;367:825.

Induction Therapy: Nontransplant Candidates
Melphalan, Prednisone, Thalidomide (MPT)



Reprinted from *The Lancet*, Vol. 367, Palumbo A et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Pgs 825-831, ©2006, with permission from Elsevier.

MP vs MP-T and MP vs Mel-100 in Newly Diagnosed Elderly MM Patients

IFM 99-06 Trial Design

Newly diagnosed MM patients

Age 65–75 yr

(N=447)

3 → **MP Arm (n=196)**
Standard MP
12 courses at 6-wk intervals

2 → **MP-T Arm (n=125)**
MP Arm + Thal at MTD but ≤400 mg/day, stopped at end of MP

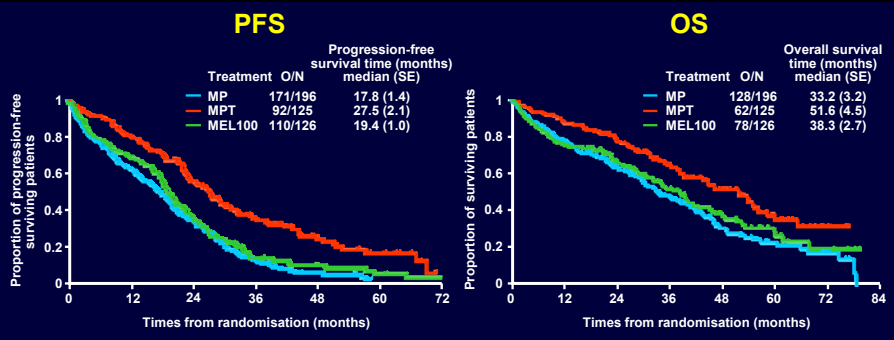
2 → **MEL-100 Arm (n=126)**
VAD×2; Cyclophosphamide 3 g/m^2 + G-CSF + PBSC harvest; (Melphalan, 100 mg/m^2 + PBSC + G-CSF)×2

1° End point: Overall survival

All patients received clodronate.

Facon T et al. *Lancet*. 2007;370:1209.

MP vs MP-T and MP vs Mel-100 in Newly Diagnosed Elderly MM Patients: Response



Treatment	PFS (mo)	*P* value	OS (mo)	*P* value
MP	17.8 ± 1.4	<0.0001	33.2 ± 3.2	0.0006
MP-T	27.5 ± 2.1	0.0002	51.6 ± 4.5	0.027
MEL-100	19.4 ± 1.0		38.3 ± 2.7	

Reprinted from *The Lancet*, Vol. 370, Facon T et al, Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone, or reduced-intensity autologous stem cell transplantation in elderly patients wtih multiple myeloma (IFM 99-06): a randomised trial. Pgs 1209-1218, ©2007, with permission from Elsevier.

Melphalan-prednisone-thalidomide (MP-T) demonstrates a significant survival advantage in elderly patients >75 yr with multiple myeloma compared with melphalan-prednisone (MP) in a randomized, double-blind, placebo-controlled trial, IFM 01/01

C. Hulin, T. Facon, P. Rodon, B. Pegourie, L. Benboubker, C. Doyen, M. Dib, G. Guillerm, L. Voillat, C. Mathiot, P. Casassus, O. Decaux, M. Flesch, L. Garderet, P. Moreau, on behalf of the Intergroupe Francophone du Myelome (IFM)

IFM 01/01 Study Protocol

Newly Diagnosed MM Pts >75 yr

Double-Blind

12 cycles MP
every 6 weeks

Melphalan
0.2 mg/kg/d days 1−4

Prednisone
2 mg/kg/d days 1−4

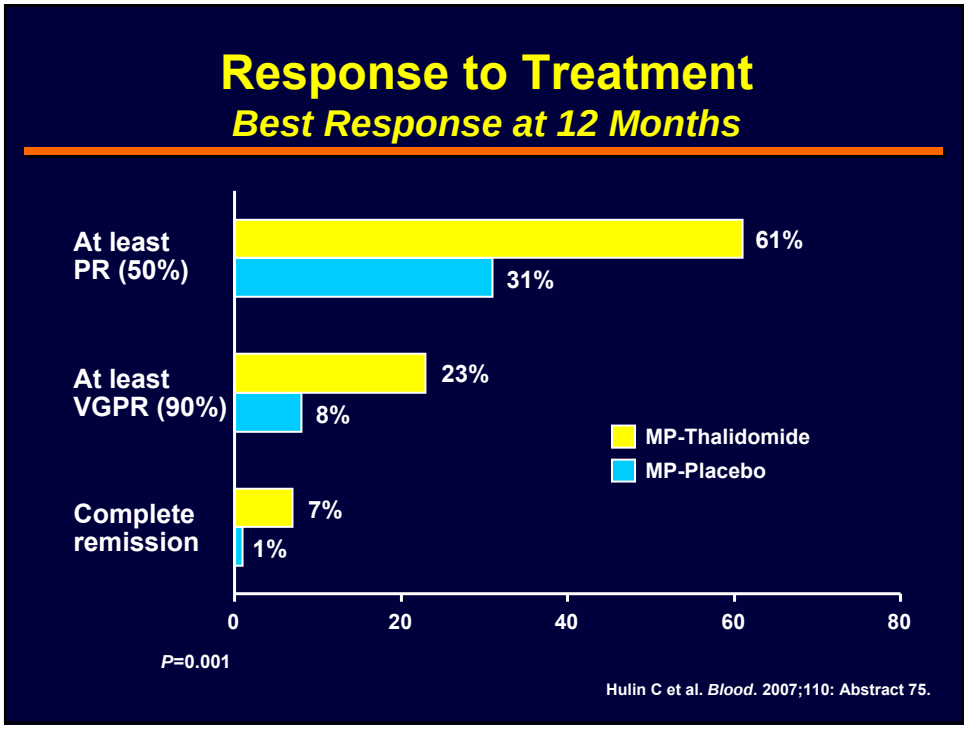
\+

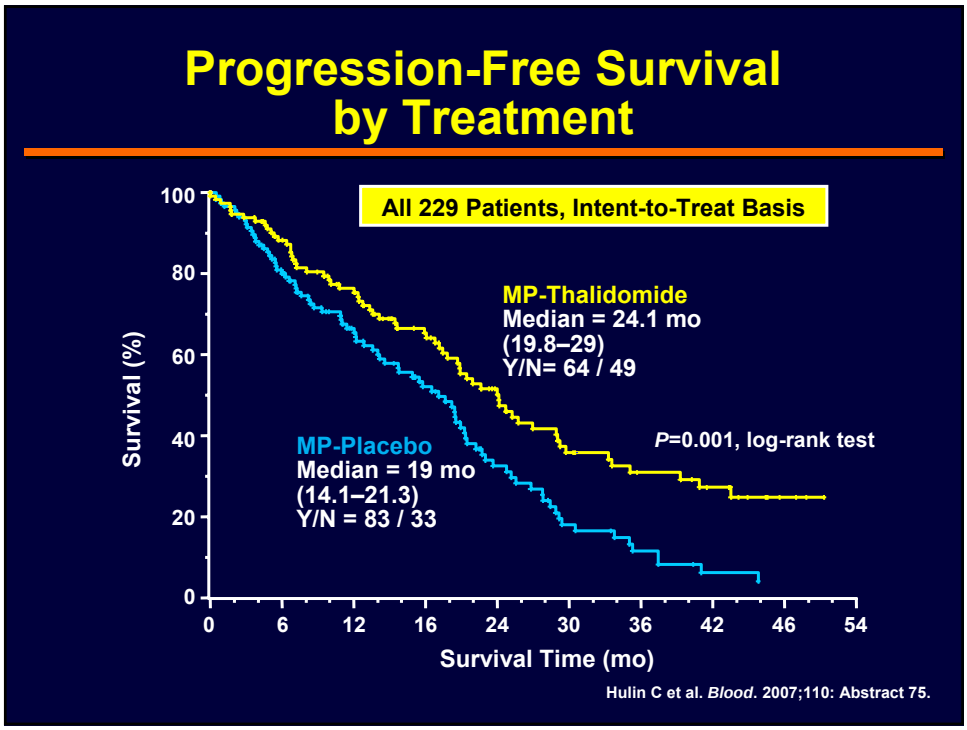
Placebo
2 caps 50 mg/d
18 months, continuously

Thalidomide
2 caps 50 mg/d
18 months, continuously

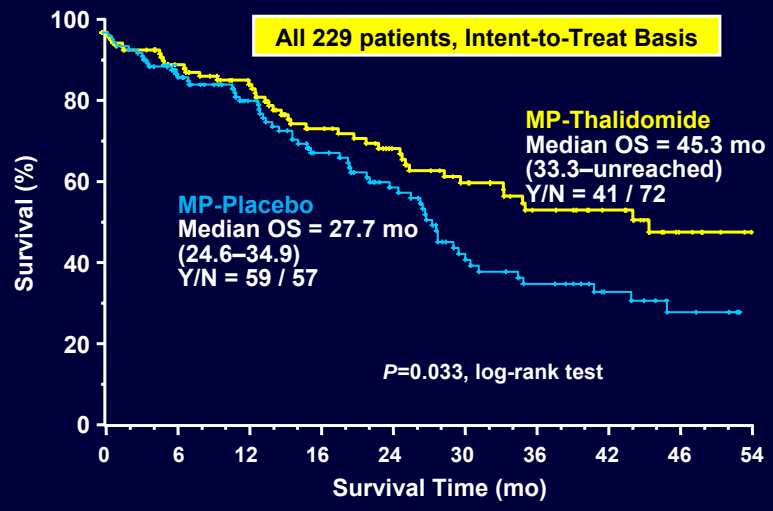
Clodronate was given to all pts.
No anticoagulant prophylaxis was planned.

Hulin C et al. *Blood*. 2007;110: Abstract 75.


Response to Treatment
Best Response at 12 Months
At least PR (50%)
61%
31%
At least VGPR (90%)
23%
8%
Complete remission
7%
1%
MP-Thalidomide
MP-Placebo
0
20
40
60
80
P=0.001
Hulin C et al. Blood. 2007;110: Abstract 75.

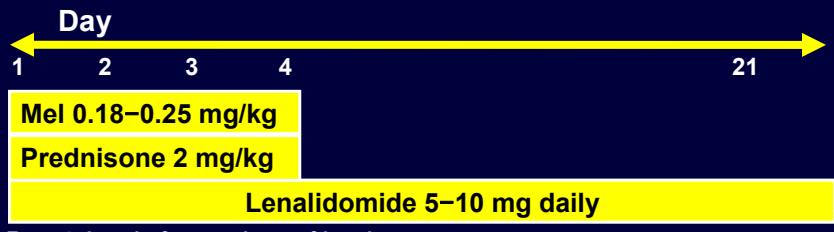

Progression-Free Survival by Treatment
All 229 Patients, Intent-to-Treat Basis
MP-Thalidomide
Median = 24.1 mo
(19.8–29)
Y/N= 64 / 49
MP-Placebo
Median = 19 mo
(14.1–21.3)
Y/N = 83 / 33
P=0.001, log-rank test
Survival (%)
100
80
60
40
20
0
0
6
12
16
24
30
36
42
46
54
Survival Time (mo)
Hulin C et al. Blood. 2007;110: Abstract 75.

Overall Survival by Treatment



Hulin C et al. *Blood*. 2007;110: Abstract 75.

R-MP: Treatment Schedule



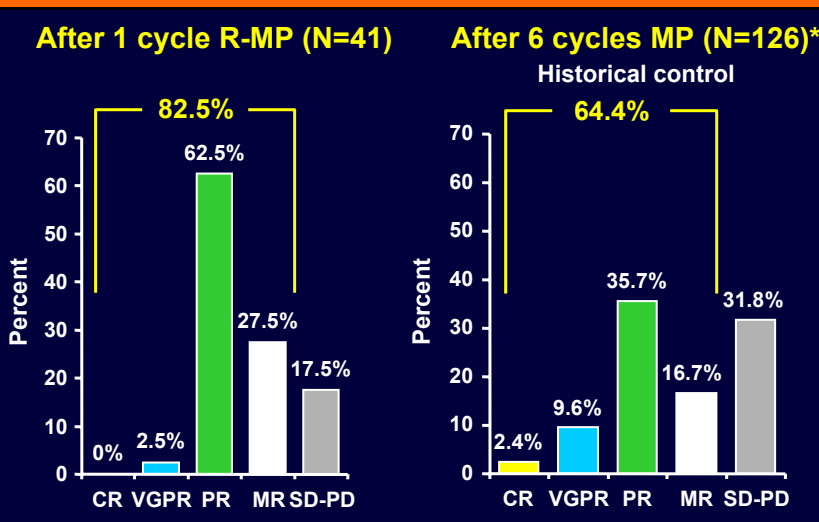
Every 4–6 weeks for a maximum of 9 cycles

	Mel (mg/kg/d)	Lenalidomide (mg/d)	Patients
Cohort 1	0.18	5	6
Cohort 2	0.25	5	6
Cohort 3	0.18	10	6 + 15
Cohort 4	0.25	10	6 + 15

6 patients in each cohort, with additional 15 patients in cohorts 3 and 4

Palumbo A et al. *Blood*. 2006;108:240a. Abstract 800.

R-MP vs MP: Response Rate

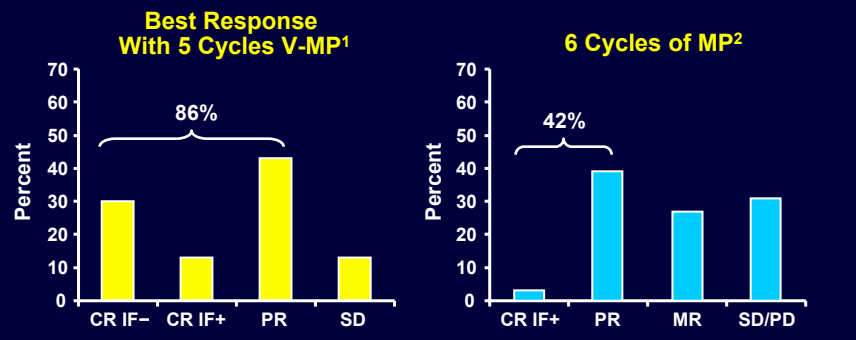


Palumbo A et al. *Blood*. 2006;108:240a. Abstract 800.

*Palumbo A et al. *Lancet*. 2006;367:825.

V-MP for Newly Diagnosed Multiple Myeloma: Response

- Best ORR: 86% (N=53) following a median of 5 cycles
- CR: 30% (6/12 or 50%; CR=immunophenotypic remission); nCR: 13%; PR: 43%
- 18-mo EFS: 18%; PFS: 93% (median follow-up at 10.5 mo)



IF, immunofixation

1. Mateos MV et al. *Blood*. 2006;108:2165.
2. Hernandez JM et al. *Br J Haematol*. 2004;127:159.

VISTA Trial

- Randomized, international, phase 3 trial of VMP vs MP in previously untreated MM patients who were not candidates for HDT-ASCT
- Patients: Symptomatic MM/end-organ damage with measurable disease
  - ≥65 yr or <65 yr and not transplant-eligible; KPS ≥60%

RANDOMIZE

VMP
Cycles 1−4
Bortezomib 1.3 mg/m² IV: days 1,4,8,11,22,25,29,32
Melphalan 9 mg/m² and prednisone 60 mg/m² days 1−4
Cycles 5−9
Bortezomib 1.3 mg/m² IV: days 1,8,22,29
Melphalan 9 mg/m² and prednisone 60 mg/m² days 1−4

9 × 6-week cycles (54 weeks) in both arms

MP
Cycles 1−9
Melphalan 9 mg/m² and prednisone 60 mg/m² days 1−4

- Primary end point: TTP
- Secondary end points: CR rate, ORR, TTR, DOR, PFS, TNT, OS, QoL (PRO)

San Miguel JF et al. *N Engl J Med.* 2008;359:906.

VISTA Trial Results

- 682 patients randomized from December 2004 to September 2006 from 151 centers in 22 countries worldwide
- IDMC recommended study stop in September 2007
  - Based on protocol-specified interim analysis (data cut-off: June 15, 2007)
  - VMP was significantly superior for all efficacy end points

Efficacy End Point	HR	*P* Value
TTP	0.48	<0.001
PFS	0.56	<0.001
OS	0.61	0.008
TNT	0.52	<0.001

*Odds ratio.

San Miguel JF et al. *N Engl J Med.* 2008;359:906.

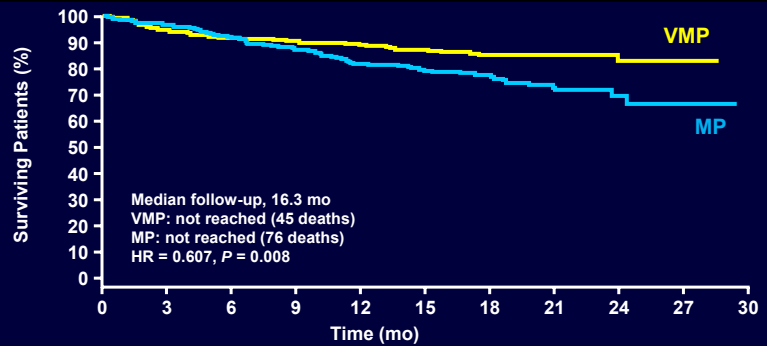
VISTA Trial Response to Treatment
High CR With VMP

	VMP (N=337)		MP (N=331)		*P* Value
	M-protein*	EBMT[1]	M-protein	EBMT[1]	
ORR (CR+PR)	74%	71%	39%	35%	<0.001
CR (IF−)	33%	30%	4%	4%	<0.001
PR	33%	40%	31%	31%	
VGPR (≥90% ↓M-protein)	8%	N/A	4%	N/A	

*International Uniform Response Criteria.

1. Bladé J et al. *Br J Haematol.* 1998;102:1115.
San Miguel JF et al. *N Engl J Med.* 2008;359:906.

VISTA Trial: Overall Survival
~40% Reduced Risk of Death on VMP



Number of patients at risk

MP:	338	320	301	280	220	157	116	69	29	7
VMP:	344	315	300	290	235	168	115	72	36	4

- OS at 2 yr: 82.6% in VMP vs 69.5% in MP
  - <75 yr: 84% in VMP vs 74% in MP
  - ≥75 yr: 79% in VMP vs 60% in MP
- Treatment-related deaths on each arm: 1% in VMP; 2% in MP

San Miguel JF et al. *N Engl J Med.* 2008;359:906.

Comparisons Among Trials

Study	Regimen	N	CR (IF−)	TTP PFS/EFS	Overall Survival
San Miguel VISTA[1]	VMP (54-wk Tx) MP (54-wk Tx)	344 338	33% (30%) 4% (4%)	24.0 mo 16.6 mo	HR=0.61 *P*=0.008
Palumbo[2]	MPT (T mainten.*) MP (no mainten.)	129 126	15.5% 2.4%	29.2 mo 13.6 mo	NS (*P*=0.19)
Facon[3]	MPT (72-wk Tx) MP (72-wk Tx)	125 196	13% 2%	27.5 mo 17.8 mo	51.6 mo vs 33.2 mo HR=0.59, *P*=0.0006
Hulin[4]	MPT (72-wk Tx) MP (72-wk Tx)	113 116	7% 1%	24.1 mo 19 mo	45.3 mo vs 27.7 mo HR=n/a, *P*=0.03

*Treat to progression.

- TTP/PFS/EFS are highly sensitive to definition and measurements

1. San Miguel JF et al. *N Engl J Med.* 2008;359:906.
2. Palumbo A et al. *Lancet.* 2006;367:825.
3. Facon T et al. *Lancet.* 2007;370:1209.
4. Hulin C et al. *Blood.* 2007;110: Abstract 75.

ECOG

Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group

S. Vincent Rajkumar, Susanna Jacobus, Natalie Callander, Rafael Fonseca, David Vesole, Michael Williams, Rafat Abonour, David Siegel, and Philip Greipp

Mayo Clinic, Rochester, MN; Dana Farber Cancer Institute, Boston, MA; University of Wisconsin, Madison, WI; Mayo Clinic Arizona, Scottsdale, AZ; St. Vincent's Hospital, New York, NY, University of Virginia, Charlottesville, VA; Indiana University, Indianapolis, IN; Hackensack University Medical Center, Hackensack, NJ

Rajkumar SV et al. *Blood*. 2007;110: Abstract 74.
Rajkumar SV et al. *J Clin Oncol*. 2008;26. Abstract 8504.

Serious Adverse Events
Non-Hematologic

	Toxicity		
	Arm A (n=222)	Arm B (n=219)	Fishers Exact *P* Value
Type (Grade 3+)	%	%	
DVT/PE	25	9	<0.001
Infection/Pneumonia	14	7	0.030
Fatigue	13	10	0.294
Hyperglycemia	11	6	0.126
Non-neuropathic weakness	10	4	0.008
Cardiac ischemia	3	0.5	0.068
Atrial fib/flutter	3	0.5	0.122
Neuropathy	2	1.5	1.000

Rajkumar SV et al. *Blood*. 2007;110: Abstract 74.
Rajkumar SV et al. *J Clin Oncol*. 2008;26. Abstract 8504.

Survival Rate by Age

	N	12-Month Survival Probability (95% CI)	24-Month Survival Probability (95% CI)
Age <65 yr			
Len + High Dex	104	0.92 (0.87–0.97)	0.85 (0.78–0.93)
Len + Low Dex	108	0.97 (0.94–1.00)	0.91 (0.84–0.98)
		P=0.13	*P*=0.16
Age ≥65 yr			
Len + High Dex	119	0.84 (0.77–0.91)	0.67 (0.56–0.77)
Len + Low Dex	114	0.95 (0.84–1.00)	0.82 (0.74–0.91)
		P=0.01	*P*=0.009

Rajkumar SV et al. *Blood*. 2007;110: Abstract 74.
Rajkumar SV et al. *J Clin Oncol*. 2008;26. Abstract 8504.

Why Melphalan Based

- Improved OS for MPT and MPV when compared to MP
- Thal/Dex is actually worse than MP in randomized comparison
- Dex based inductions carry higher toxicity and do not improve OS
- Burden of Proof for non MP based inductions should be to beat MPT or MPV

Why Not Melphalan Based

- Hematology toxicity related to Mel is more pronounced in older patients
- Cannot 'take back' Melphalan once given, and effects can be long lasting
- Melphalan alone is not as effective in the setting of high risk disease, which is seen in 30% of newly diagnosed patients.
- Novel agents used without Melphalan may be safer, but need to be proven superior before widespread adoption

Conclusions

- MP + novel agent is superior to MP alone
- Need less-toxic inductions for these elderly patients
- There is still a benefit for achieving a CR, if it can be done with tolerability
- Risk stratification may be of benefit in this population as well
- New approaches using non−MP-based inductions are interesting, but need phase 3 follow-up in order to be proven