

Role of Bortezomib in the treatment of elderly newly diagnosed myeloma

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Background

- **Bortezomib**: Significant activity as monotherapy in relapsed/refractory MM^{5,6}
 - *In vitro* synergy in combination with cytotoxic agents such as melphalan⁷
- Our **phase I/II PETHEMA/GEM study** showed that bortezomib plus MP (VMP) resulted in rapid and durable responses^{8,9}
 - 89% ≥PR with **32% CR rate**
 - Median time to progression (TTP) was **27.2 months**^{8,9}
 - Median OS was **58 months** (vs 29 m for historical MP)¹⁰
 - **VMP was well tolerated**; patients remained on therapy for a median of 9 months⁸

1. Palumbo et al. *Lancet* 2006;367:826-3.
2. Facon et al. *Lancet* 2007;370:1209-1218.
3. Myeloma Trialists' Collaborative Group. *JCO* 1998;16:3832-42.
4. Waage et al. *Blood* 2007;110:1802-1810.
5. Richardson et al. *N Engl J Med* 2003;348:2486.
6. Richardson et al. *N Engl J Med* 2005;352:2487.
7. Ma et al. *Clin Cancer Res* 2003;9:1138.
8. Mateos et al. *Blood* 2006;108:2166-72.
9. Mateos et al. *Hematologica* 2008;93:590-5.
10. Hernandez et al. *Br J Haematol* 2004;127:159-64.

VISTA: VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone

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

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VMP
Cycles 1–4
Bortezomib 1.3 mg/m² IV, d 1,4,8,11,22,25,29,32
Melphalan 9 mg/m² IV, and prednisone 60 mg/m² IV, d 1–4
Cycles 5–9
Bortezomib 1.3 mg/m² IV, d 1,8,22,29
Melphalan 9 mg/m² IV and prednisone 60 mg/m² IV, d 1–4
9 x 6-week cycles (54 weeks) in both arms

► Primary end point: TTP
► Secondary end points: CR rate, ORR, time to response, DOR, time to next therapy, OS, PFS, QoL (PRO)

MP
Cycles 1–9
Melphalan 9 mg/m² IV and prednisone 60 mg/m² IV, d 1–4

- Stratification: β_2 -microglobulin, albumin, region

Response to treatment High CR rate with VMP

	VMP, N=337		MP, N=331		p-value
	EBMT ¹	Uniform ^{2†}	EBMT ¹	Uniform ^{2†}	
ORR (≥PR)	71%	74%	35%	39%	<10 ⁻⁶
CR	30%	33%	4%	4%	<10 ⁻⁶
VGPR	NA	8%	NA	4%	
PR	40%	33%	31%	31%	
MR	9%	NA	22%	NA	
SD	18%	23%	40%	58%	

With VMP, 79 patients (23%) had SD by Uniform criteria; 4 (1%) were CR, and 19 (6%) PR but confirmatory test^{*} was missing. If these patients were included, response rate was: **82% ≥PR with 35% CR**
In addition, 38 (11%) patients had MR by EBMT criteria; accordingly, **only 18 (5%) patients were 'true' non-responders with VMP**

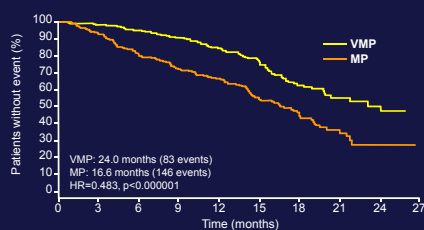
^{*}CT or Urine

[†]Post-hoc analysis by International Uniform Response Criteria²

1. Bladé et al. *Br J Haematol* 1998;102:1115-23
2. Durie et al. *Leukemia* 2009;23:1467-73

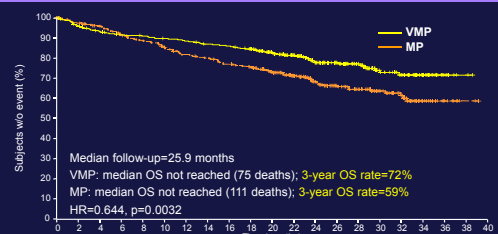
San Miguel et al. *N Engl J Med* 2008;359:906-17

Time to progression: ~52% reduced risk of progression with VMP

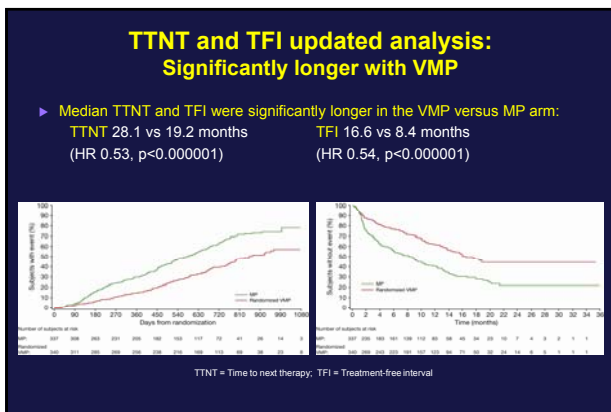
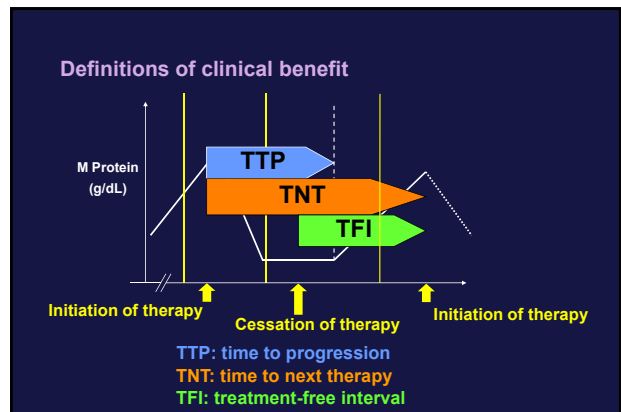
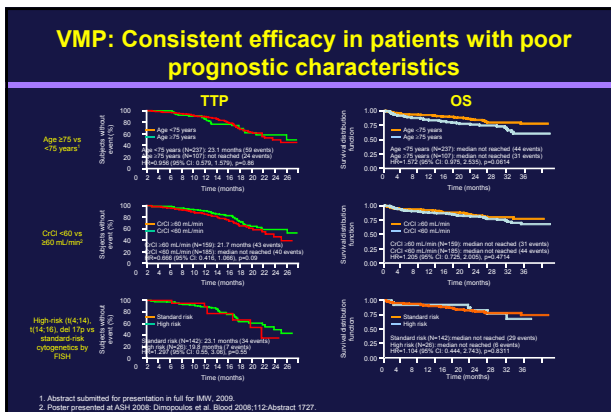


San Miguel et al. *N Engl J Med* 2008;359:906-17; EHA 2008;110:Abstract 473

OS: Confirmed survival benefit with VMP ~36% reduced risk of death on VMP



- 43% of MP patients who received subsequent therapy **received bortezomib upon progression**
- Patients received bortezomib >4 cycles: OS at 1 & 2 years: 98.5% & 89%



Subsequent therapy

- Fewer patients in the VMP versus MP arm (38% vs 57%, respectively) had required subsequent therapy by the time of data cut-off

	VMP (N=129)	MP (N=194)
Bortezomib, n (%)	21 (16)	84 (43)
Thalidomide, n (%)	63 (49)	86 (44)
Lenalidomide, n (%)	25 (19)	12 (6)
Others*, n (%)	20 (16)	12 (6)

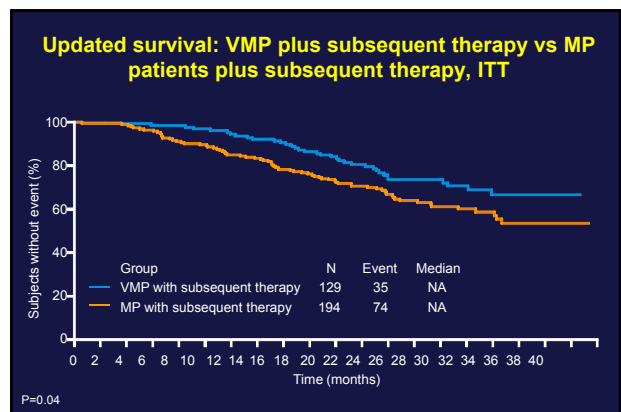
* Other agents were used as subsequent therapy, including dexamethasone; patients could receive multiple-agent regimens.

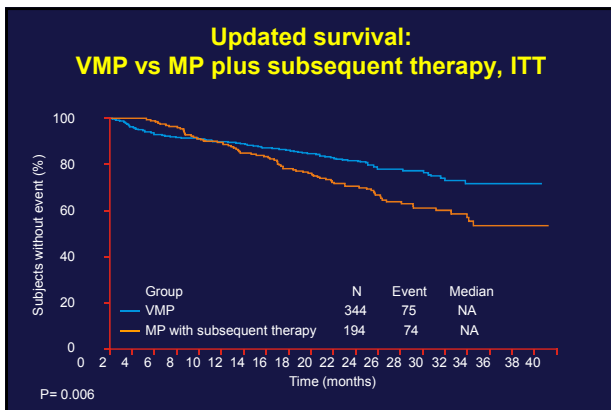
Investigator-reported best responses with subsequent therapies per treatment arm

Subsequent therapy and number of patients who received therapy*	VMP (N=129)		MP (N=194)	
	CR (%)	PR (%)	CR (%)	PR (%)
Bortezomib** or bortezomib combination (n=105)	6	n=21 33	10	n=84 45
Thalidomide** or thalidomide combination (n=149)	4	n=63 44	3	n=86 52
Lenalidomide** or lenalidomide combination (n=37)	4	n=25 52	0	n=12 55

*Other agents were used as subsequent therapy, including dexamethasone; patients could receive multiple-agent regimens.
** Single-agent use: 36% bortezomib, 37% thalidomide, 14% lenalidomide

- Patients relapsing after VMP are not intrinsically more resistant than after using a traditional MP:
 - Use of bortezomib does not preclude use of IMiDs at relapse
 - Re-treatment with bortezomib is feasible



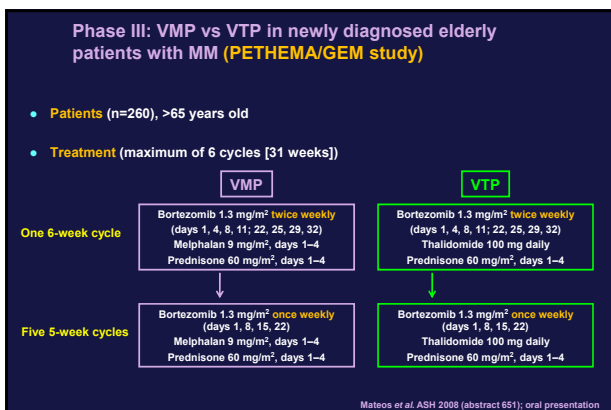
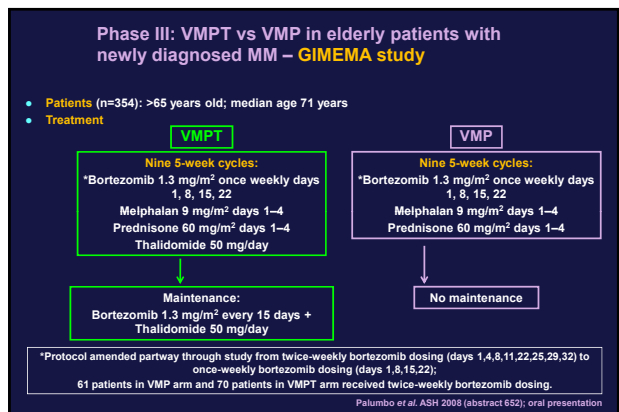


Adverse events: Updated data

AE, %	VMP (N=340)		MP (N=337)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	29	11	23	15
Thrombocytopenia	20	18	16	15
Anemia	16	3	20	8
Gastrointestinal	19	1	5	0
Peripheral sensory neuropathy	13	<1	0	0
Fatigue	7	1	2	0
Asthenia	6	<1	3	0
Pneumonia	5	2	4	1
Herpes zoster	4	0	2	0

- ▶ **Herpes zoster** was more frequent with VMP (14% vs 4%)
 - Rate with VMP was only 3% among patients receiving **antiviral prophylaxis**
- ▶ **Peripheral neuropathy** was manageable and reversible
 - 79% of PN events improved (≥1 grade), median of 1.9 months
 - 60% of PN events completely resolved, median of 5.7 months
- ▶ Among patients who developed treatment-emergent PN while on VMP, 19% were treated with subsequent bortezomib, 48% subsequent thalidomide, and 33% subsequent lenalidomide

Are there any other modified bortezomib-based combinations for elderly untreated MM patients?



Overview of bortezomib doses and response data in Phase III trials

Study	n	Bortezomib schedule	Planned treatment	CR (IF- (VMP arm))	TTP, OS
VISTA: VMP vs MP San Miguel et al. N Engl J Med 2008;359:906–917	337 vs 331	Four 6-week cycles 1.3 mg/m ² , d 1, 4, 8, 11, 22, 25, 29, 32 Five 6-week cycles 1.3 mg/m ² , d 1, 8, 22, 29	54 weeks: 52 bortezomib dosages	30%	TTP: 24 months OS: median not reached at 25.9 months 3-year OS: 72%
VMPT vs VMP Palumbo et al. ASH 2008 (abstract 652)	177 vs 177	Four 6-week cycles 1.3 mg/m ² , d 1, 4, 8, 11, 22, 25, 29, 32 Five 6-week cycles 1.3 mg/m ² , d 1, 8, 22, 29 From March 2007: Nine 5-week cycles Bortezomib 1.3 mg/m ² , d 1, 8, 15, 22	54 weeks: 52 bortezomib dosages 45 weeks: 38 bortezomib dosages	20%	Median TTP and OS not yet available VMPT 3-year PFS: 75% VMP 3-year PFS: 70%
VMP vs VTP Mateos et al. ASH 2008 (abstract 651)	130 vs 130	One 6-week cycle 1.3 mg/m ² , days 1, 4, 8, 11, 22, 25, 29, 32 Five 5-week cycles 1.3 mg/m ² , days 1, 8, 15, 22	31 weeks: 28 bortezomib dosages	22%	Median TTP and OS not yet available 2-year TTP: 72% 2-year OS: ~90%

Overview of bortezomib doses and adverse event data in Phase III trials

Study	n	Bortezomib schedule	Planned treatment	PN (grade 3/4)	Discontinuation
VISTA: VMP vs MP San Miguel et al. <i>N Engl J Med</i> 2008;359:906-17	337 vs 331	Four 6-week cycles 1.3 mg/m ² , d 1, 4, 8, 11, 22, 25, 29, 32 Five 6-week cycles 1.3 mg/m ² , d 1, 8, 22, 29	54 weeks: 52 bortezomib dosages	14%	19%
VMP vs VMP Palumbo et al. ASH 2008 (abstract 652)	177 vs 177	Four 6-week cycles 1.3 mg/m ² , d 1, 4, 8, 11, 22, 25, 29, 32 Five 6-week cycles 1.3 mg/m ² , d 1, 8, 22, 29 From March 2007: Nine 5-week cycles Bortezomib 1.3 mg/m ² , d 1, 8, 15, 22	54 weeks: 52 bortezomib dosages 45 weeks: 38 bortezomib dosages	2%	10%
VMP vs VTP Maitos et al. ASH 2008 (abstract 651)	130 vs 130	One 6-week cycle 1.3 mg/m ² , days 1, 4, 8, 11, 22, 25, 29, 32 Five 5-week cycles 1.3 mg/m ² , days 1, 8, 15, 22	31 weeks: 28 bortezomib dosages	5%	8%

Conclusions

- MP + Bortezomib improves outcome for patients not eligible for transplantation
 - **VISTA trial** demonstrated that VMP was significantly superior over MP in terms of OS, TTP, and CR: **Consolidate data.**
- Longer follow up needed to obtain PFS and OS data in trials investigating VMP schedule with reduced bortezomib dose