# Treatment of newly diagnosed patients with Multiple Myeloma with Bortezomib based regimens

## a focus on European practice

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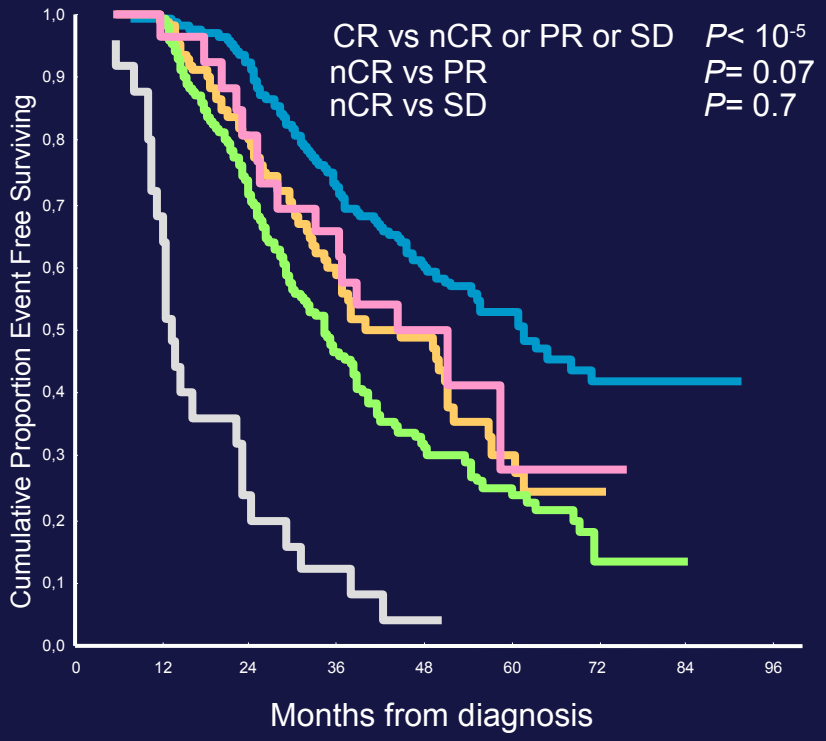
# Importance of achieving complete response: A new aim for using *novel* agents

## Study details (n=632)

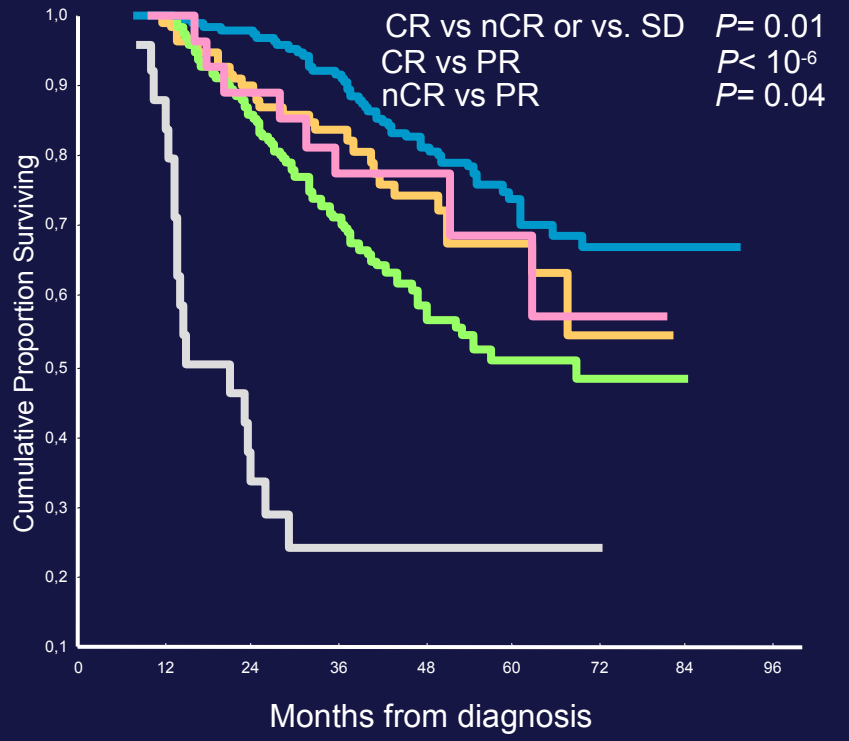
- **VBCMP/VBAD induction, HDT + ASCT, maintenance interferon + prednisone**

## Outcome according to post-transplant response

EFS




OS




CR, n= 278 nCR, n=124 PR, n=280 SD, n=30 PD, n=25

Lahuerta *et al.*; *J Clin Oncol* 2008;26:5775–82

# Part 1
# Newly diagnosed MM patients eligible for transplantation

# Improving ASCT outcomes in eligible patients

- VAD has been a long-standing standard induction prior to ASCT

  ***but:*** - CR rate only 5–10%[1]

  - Treatment-related mortality (2–5%) in high risk patients: 30–35% of patients receive no SCT due to progression/infection[5]

- CR + VGPR following ASCT is associated with prolonged EFS and OS[2]

- Aim: To improve CR rates pre- and post-transplant using novel agents as part of induction regimen[2,3]

- Improving CR + VGPR rate following induction could result in further improved long-term outcomes[2,4]


1. Reece. *Hematology* 2005;353–359
2. Harousseau. *Ann Oncol* 2002;13(Suppl. 4):49–54
3. Attal *et al. Hematology* 2007;311–316
4. Jagannath. Ha*ematologica* 2007;92(Suppl. 2) (Abstract S5.3)
5. Moreau et al. Blood 2006

# Thalidomide-based induction regimens

| | Macro[1] ThalDex vs VAD (n=100 vs 104) | Morgan[2] CTD vs CVAD (n=124 vs 127) | Lokhorst[3] TAD vs VAD (n=201 vs 201) |
|---|---|---|---|
| # induction Cycles | 4 | 4–6 | 3 |
| **Results post-induction** | | | |
| CR + nCR | – | 19% vs 9%* | 4% vs 2%* |
| ≥VGPR | 35% vs 13% | 39% vs 27% | 33% vs 15% |
| CR + PR | – | 87% vs 75% | 77% vs 54% |
| **Results post-ASCT** | | | |
| CR + nCR | – | 51% vs 40%* | 30% vs 21%* |
| ≥VGPR | 44% vs 42% | 67% vs 53% | 65% vs 54% |
| CR + PR | – | 88% vs 87% | 87% vs 79% |

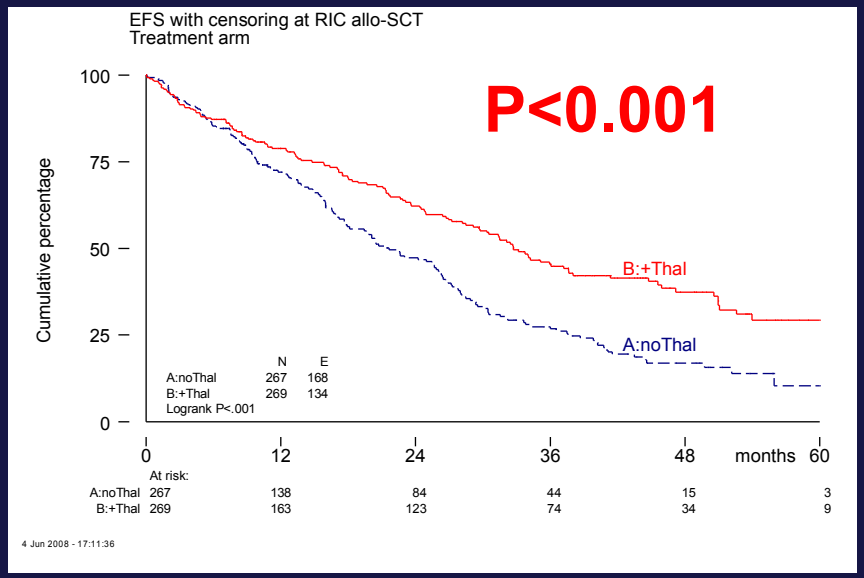
*CR only

- **TAD vs VAD**
  (ASH 2008, IMW 2009)[4]
  - Significantly better ORR, EFS and PFS with TAD; but not OS
  - EFS: 33 vs 22 months, *P*<0.001
  - PFS: 33 vs 25 months, *P*<0.001
  - OS: 59 vs 62 months, *P*=0.96

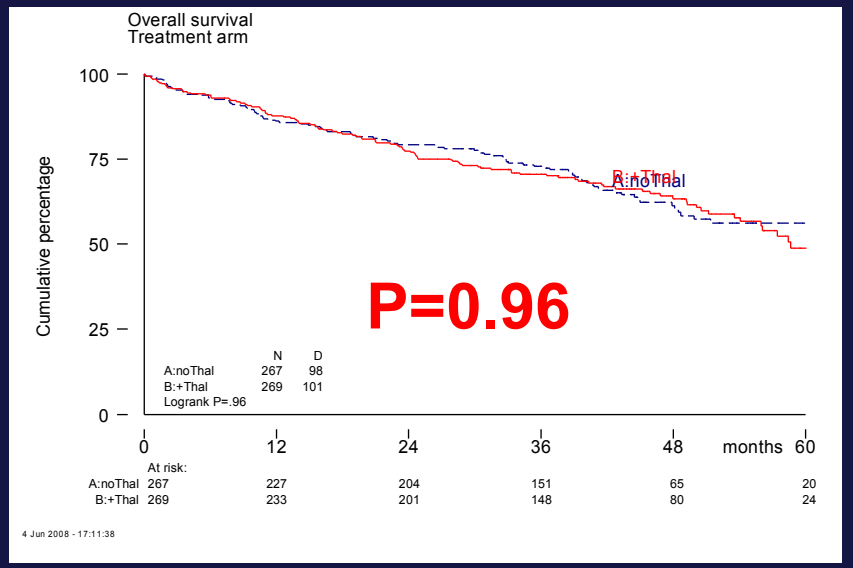

1. Macro et al. ASH 2006 (Abstract 57)
2. Morgan et al. ASH 2007 (Abstract 3593); IMW 2009 (Abstract 546)
3. Lokhorst *et al*. *Haematologica* 2008;93:124–127
4. Lokhorst *et al*. ASH 2008 (Abstract 157); IMW 2009 (Abstract 46)

# Event Free Survival and Survival in Hovon 50

EFS




OS




Lokhorst *et al*. ASH 2008 (abstract 157); IMW 2009 (abstract 46

HOVON

# Phase III ECOG trial: RD vs Rd

## Primary therapy with RD vs Rd: 4-month landmark analysis

| | RD | | Rd |
|---|---|---|---|
| **Primary therapy: 4 cycles** | | | |
| No transplantation | n=54 | | n=39 |
| 3-year OS (%) | | <60 | |
| Transplantation | n=50 | | n=40 |
| 3-year OS (%) | | 92 | |
| **Primary therapy: > 4 cycles** | n=108 | | n=140 |
| 3-year OS (%) | | 79 | |

Rajkumar *et al.* ASH 2008 Joint ASH/ASCO symposium

# Summary of post-induction results in Phase III bortezomib trials

| | IFM 2005/01 | GIMEMA | HOVON-GMMG | PETHEMA/GEM |
|---|---|---|---|---|
| | Harousseau<br>**VD vs VAD**<br>(n=214 vs 210)<br>(ASH 2008, joint ASH/ASCO symposium) | Cavo<br>**VTD vs TD**<br>(n=226 vs 234)<br>(IMW 2009; Abstract 451) | Sonneveld<br>**PAD vs VAD**<br>(n=150 vs 150)<br>(IMW 2009; Abstract 152) | Rosinol<br>**VTD vs VBCMP/VBAD+V vs TD**<br>(n=61 vs 58 vs 61)<br>(IMW 2009; Abstract 160) |
| **Results post-induction** | | | | |
| **CR** | **6% vs 1%*** | **21% vs 6%*** | n/a | **30% vs 20% vs 6%*** |
| **CR + nCR** | **15% vs 7%*** | **32% vs 12%*** | **7% vs 2%*** | n/a |
| **≥VGPR** | **39% vs 16%*** | **62% vs 29%*** | **45% vs 17%*** | n/a |
| **CR + PR** | **82% vs 65%*** | **94% vs 79%*** | **79% vs n/a%*** | **77% vs 70% vs 62%** |

*significantly different

**Bortezomib induction regimen results in high CR/nCR rates post-induction**

n/a: not available

# Summary of post-transplant results in Phase III bortezomib trials

| | IFM 2005/01 | GIMEMA | HOVON-GMMG | PETHEMA/GEM |
|---|---|---|---|---|
| | **Harousseau**<br>**VD vs VAD**<br>(n=212 vs 213) (ASH 2008, joint ASH/ASCO symposium) | **Cavo**<br>**VTD vs TD**<br>(n=226 vs 234) (IMW 2009; Abstract 451) | **Sonneveld**<br>**PAD vs VAD**<br>(n=150 vs 150) (IMW 2009; Abstract 152) | **Rosinol**<br>**VTD vs VBCMP/VBAD+V vs TD**<br>(n=61 vs 58 vs 61) (IMW 2009; Abstract 160) |
| **Results post-ASCT** | | | | |
| **CR** | **17% vs 9%*** | **43% vs 23%*** | n/a | **48% vs 43% vs 23%** |
| **CR + nCR** | **37% vs 19%*** | **55% vs 32%*** | **26% vs 14%*** | n/a |
| **≥VGPR** | **57% vs 38%*** | **76% vs 58%*** | **71% vs 44%*** | n/a |
| **CR + PR** | **84% vs 79%** | n/a | **91% vs 79%*** | n/a |

*significantly different

**Bortezomib induction regimen results in high CR/nCR and VGPR rates post-transplant**

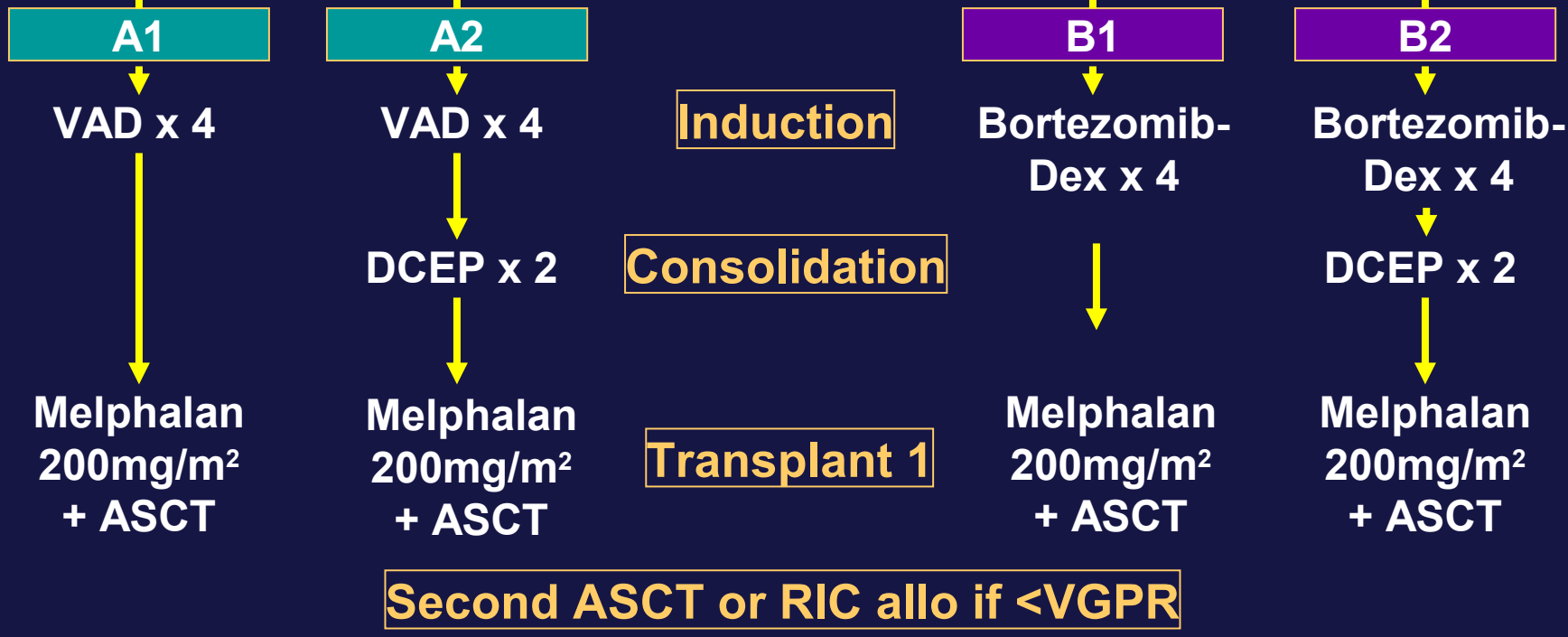
n/a: not available

# IFM 2005/01 Study: Bortezomib-Dex vs VAD

Primary analysis: post-induction response in VAD vs Bortezomib-Dex

Randomization

stratified by $\beta_2$-microglobulin level (>3mg/L vs ≤3mg/L) and presence of chromosome 13 abnormalities (by FISH analysis)




Harousseau *et al*. ASH/ASCO Joint symposium at ASH 2008

# Responses (evaluable patients)

| | VAD | Bortezomib-dex | *P* |
|---|---|---|---|
| **Response after induction** | | | |
| | n=210 | n=214 | |
| CR + nCR | 7% | 15% | 0.0035 |
| ≥VGPR | 16% | 39% | <0.0001 |
| ≥PR | 65% | 82% | <0.0001 |
| **Response after first ASCT** | | | |
| | n=213 | n=212 | |
| CR + nCR | 19% | 37% | 0.0001 |
| ≥VGPR | 38% | 57% | 0.0003 |
| ≥PR | 79% | 84% | ns |

- Bortezomib results in significantly higher CR/nCR and VGPR rates than VAD
- Response rates are improved post-ASCT

Harousseau *et al*. ASH/ASCO Joint symposium at ASH 2008

# Impact of β2M and del(13) on post-induction responses (≥VGPR)

| | Bortezomib-Dex | VAD | *P* |
|---|---|---|---|
| **Chr 13 (by FISH)** | | | |
| Deletion | n=101 | n=103 | |
| | 47% | 15% | <0.0001 |
| Normal/NE | n=139 | n=139 | |
| | 30% | 15% | 0.003 |
| **β2M≤3/Δ13** | n=63 | n=65 | |
| | 43% | 15% | 0.0006 |
| **t(4;14) and/or Δ(17p)** | | | |
| Deletion | n=40 | n=29 | |
| | 40% | 17% | 0.04 |
| Normal/NE | N=200 | n-=213 | |
| | 37% | 15% | <0.0001 |

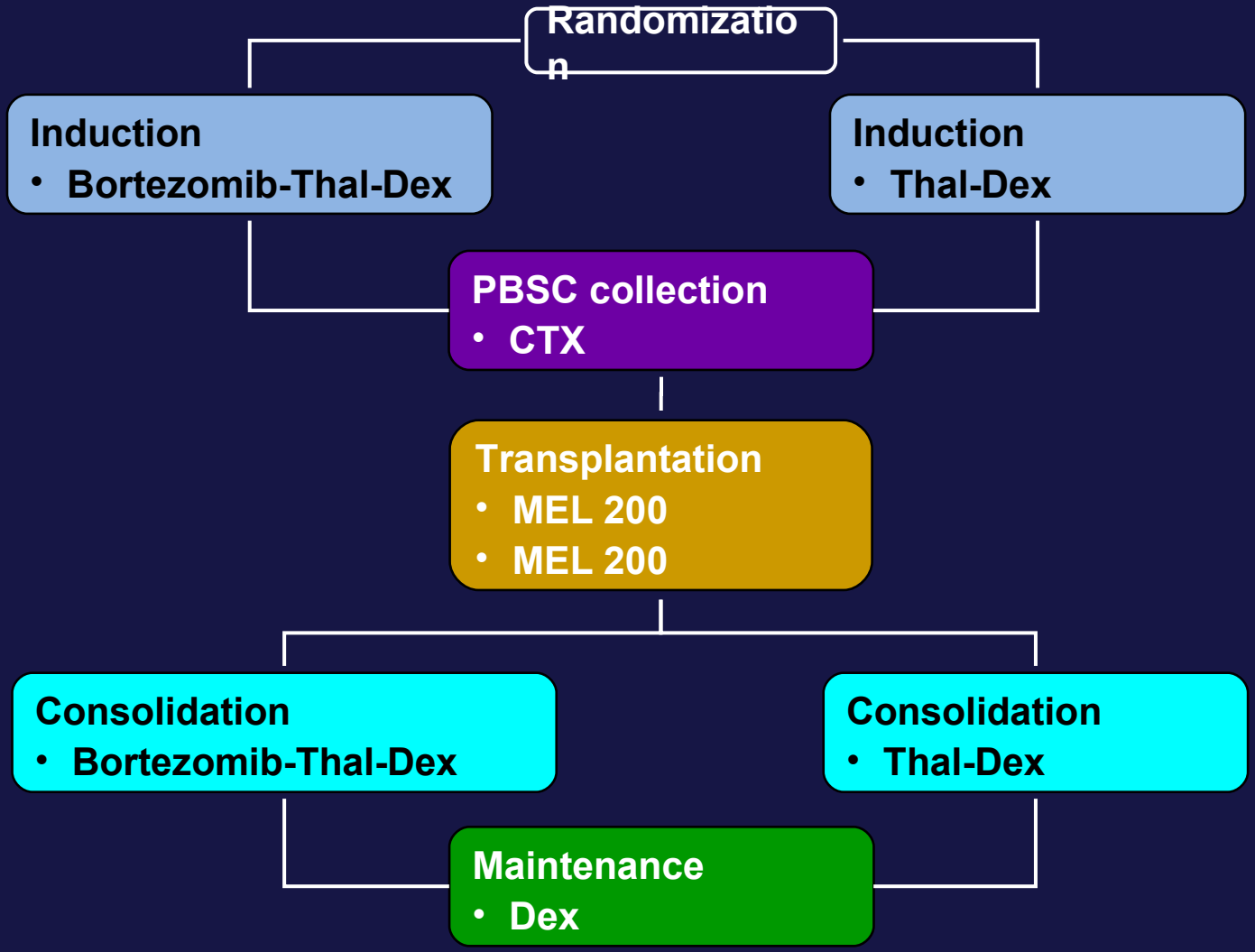
Harousseau *et al*. ASH/ASCO Joint symposium at ASH 2008

# Adverse events

| | VAD (n=239) | Bortezomib-dex (n=238) |
|---|---|---|
| Anemia (grade 3/4) | 9% | 4% |
| Neutropenia (grade 3/4) | 10% | 5% |
| Thrombocytopenia (grade 3/4) | 1% | 3% |
| Infection (grade 3/4) | 12% | 9% |
| Herpes zoster (all grades) | 2% | 9% |
| Thrombosis (all grades) | 12% | 5% |
| Fatigue (all grades) | 21% | 28% |
| Rash (all grades) | 9% | 12% |
| GI symptoms (all grades) | 31% | 27% |
| Peripheral neuropathy | | |
| Grade 2 | 8% | 18% |
| Grade 3/4 | 2% | 7% |

Harousseau *et al*. ASH/ASCO Joint symposium at ASH 2008

# Bortezomib-Thalidomide-Dex (VTD) vs Thalidomide-Dex (TD) (GIMEMA study)




Cavo *et al.* Blood 2008; 112: Abstract 158

# VTD vs TD: Response rates

| | VTD (%) n=226 | TD (%) n=234 | *P* |
|---|---|---|---|
| **Response after induction** | | | |
| CR | 21 | 6 | <0.001 |
| CR/nCR | 32 | 12 | < 0.001 |
| ≥ VGPR | 62 | 29 | < 0.001 |
| ≥ PR | 94 | 79 | <0.001 |
| Progression | 0 | 4.7 | 0.001 |
| **Responses after ASCT** | | | |
| CR | 43 | 23 | <0.001 |
| CR/nCR | 55 | 32 | < 0.001 |
| ≥ VGPR | 76 | 58 | < 0.001 |

Superiority of VTD over TD maintained across all sub-group analyses according to standard prognostic factors, including β2-m, albumin, stage (ISS), Hb, PLTs, bone marrow PC, M protein isotype, LDH, CRP

Cavo *et al.* Blood 2008; 112: Abstract 158

# Response in patients with cytogenetic abnormalities

CR+nCRs by treatment arms in relationship to cytogenetics (FISH data available in 93% to 99% of all pts)

| | VTD (%) | TD (%) | *P* |
|---|---|---|---|
| del(13) | 39% | 12% | <0.001 |
| t(4;14) | 40% | 8.5% | <0.001 |
| del(17p) | 27% | 0 | 0.03 |

Superiority of VTD over TD observed in low-risk and high-risk sub-groups, including patients with del(13), t(4,14) and del(17p)

Cavo *et al.* Blood 2008; 112: Abstract 158

# Grade 3-4 non-hematologic adverse events (induction therapy)

| Adverse Event | VTD (n=226) | TD (n=234) | *P* |
|---|---|---|---|
| SAEs | 15% | 12% | NS |
| PN | 9.1% | 2.1% | <0.001 |
| Skin Rash | 7.9% | 1.2% | <0.001 |
| DVT | 3.9% | 5.5% | NS |
| Infections (exclud. Herpes zoster) | 2.6% | 4.2% | NS |
| Constipation | 2.6% | 2.5% | NS |
| Liver Toxicity | 1.7% | 2.5% | NS |
| Herpes Zoster Infection | 1% | 0 | NS |

NS: Not significant

Cavo *et al.* Blood 2008; 112: Abstract 158

# Discontinuation of induction therapy

| | VTD (n=226) | TD (n=234) |
|---|---|---|
| Discontinuation | 4.4%* | 10.2%* |
| Toxicity | 3.1% | 2.1% |
| Progression | 0 | 4.7% |
| Other | 1.3% | 3.4% |
| Early Deaths | 0.4% | 0.9% |

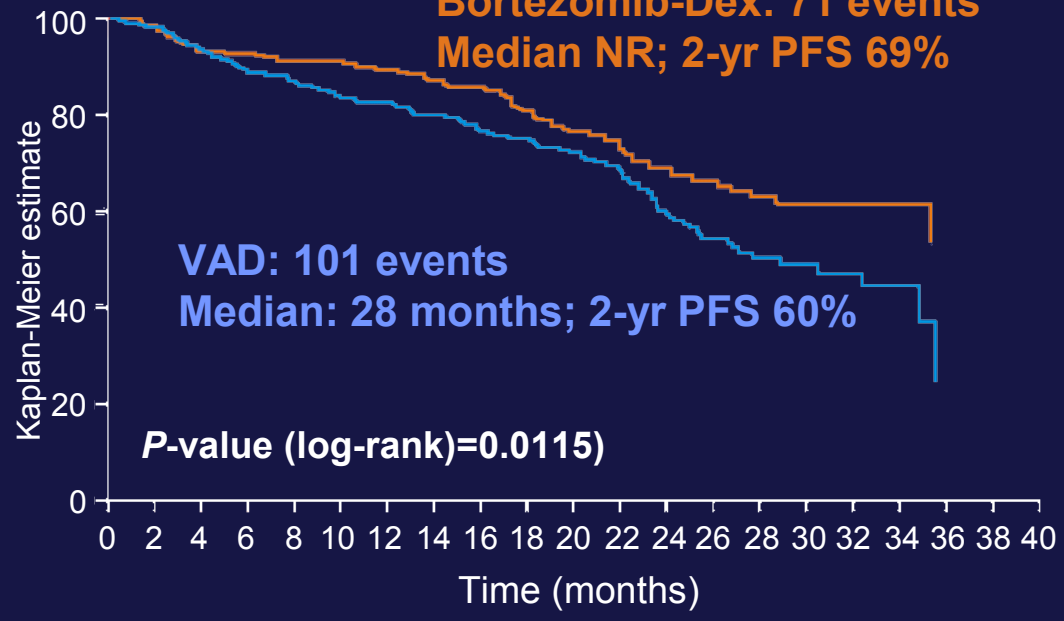
* $P$=0.01

Cavo *et al.* Blood 2008; 112: Abstract 158

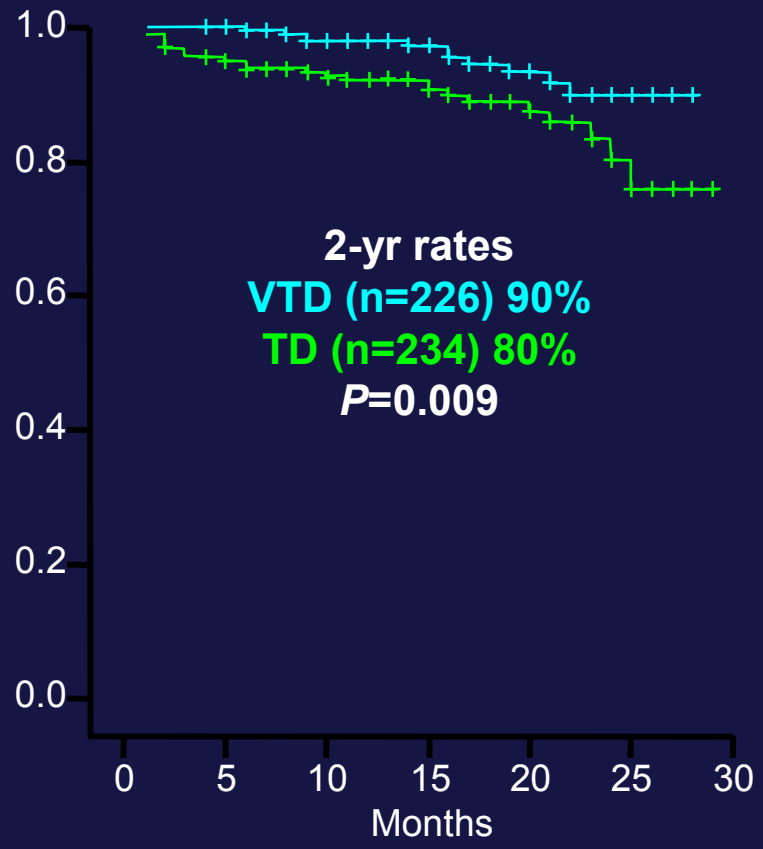
# Progression-free survival advantage with bortezomib induction regimens

**PFS data in Phase III trials**

**IFM 2005/01: Bortezomib/dex vs VAD**




**GIMEMA: VTD vs TD**

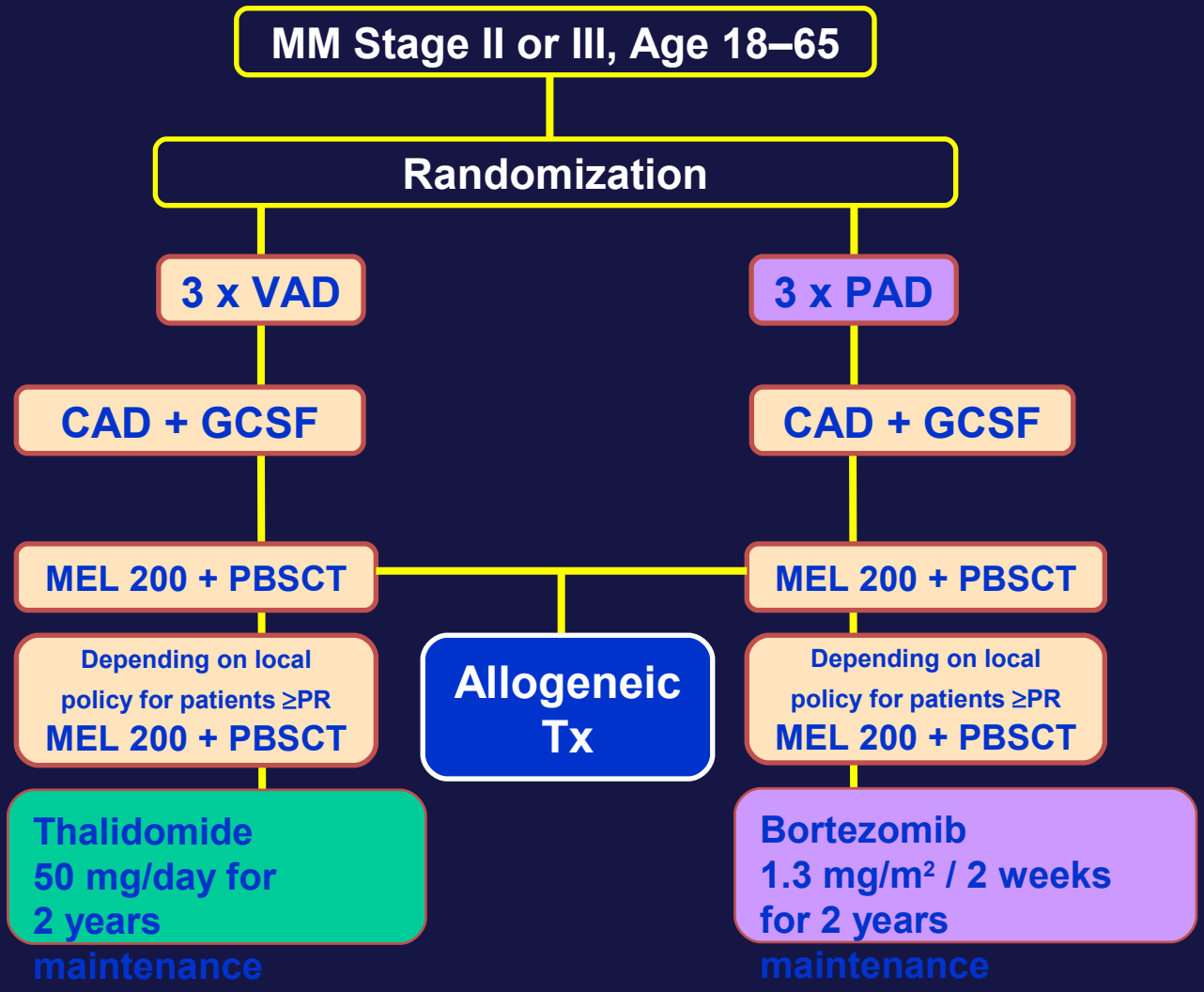



Harousseau *et al.* ASH 2008 (joint ASH/ASCO symposium)

Cavo *et al.* ASH 2008 (Abstract 158); IMW 2009 (Abstract 451)

# Phase III: PAD vs VAD as induction treatment

## HOVON 65 MM / GMMG-HD4 study




Sonneveld *et al.* EHA 2009 Abstract 473

# Response rates

**Interim analysis: n=300 with complete data set; analysis as of 26 February 2009**

| | VAD (n=150) | PAD (n=150) | *P* |
|---|---|---|---|
| **Response after induction** | | | |
| CR/nCR | 2% | 7% | * |
| ≥VGPR | 17% | 45% | * |
| ≥PR | na | 79% | * |
| **Responses after first ASCT** | | | |
| CR/nCR | 14% | 26% | * |
| ≥VGPR | 44% | 71% | * |
| ≥PR | 79% | 91% | * |

* Significant difference between arms

**PAD significantly increased the rate of CR+nCR and ≥VGPR pre- and post-transplant compared with VAD**

Sonneveld *et al.* EHA 2009 Abstract 473

# Response data

## Improvement in CR rate over course of treatment

| | | Induction | HDM | Maintenance (6 months) |
|---|---|---|---|---|
| CR/nCR | VAD | 2% | 14% | 27% |
| | PAD | 7% | 26% | 43% |

## Impact of del(13) and t(4;14) on response

| | | VAD ≥VGPR | PAD ≥VGPR |
|---|---|---|---|
| del(13) n=146 | yes / no | 66% / 56% (ns) | 81% / 66% (ns) |
| t(4;14) n=132 | yes / no | 93% / 57% * | 85% / 73% (ns) |

ns = not significantly different
* significantly different

Sonneveld *et al.* EHA 2009 Abstract 473

# Adverse events

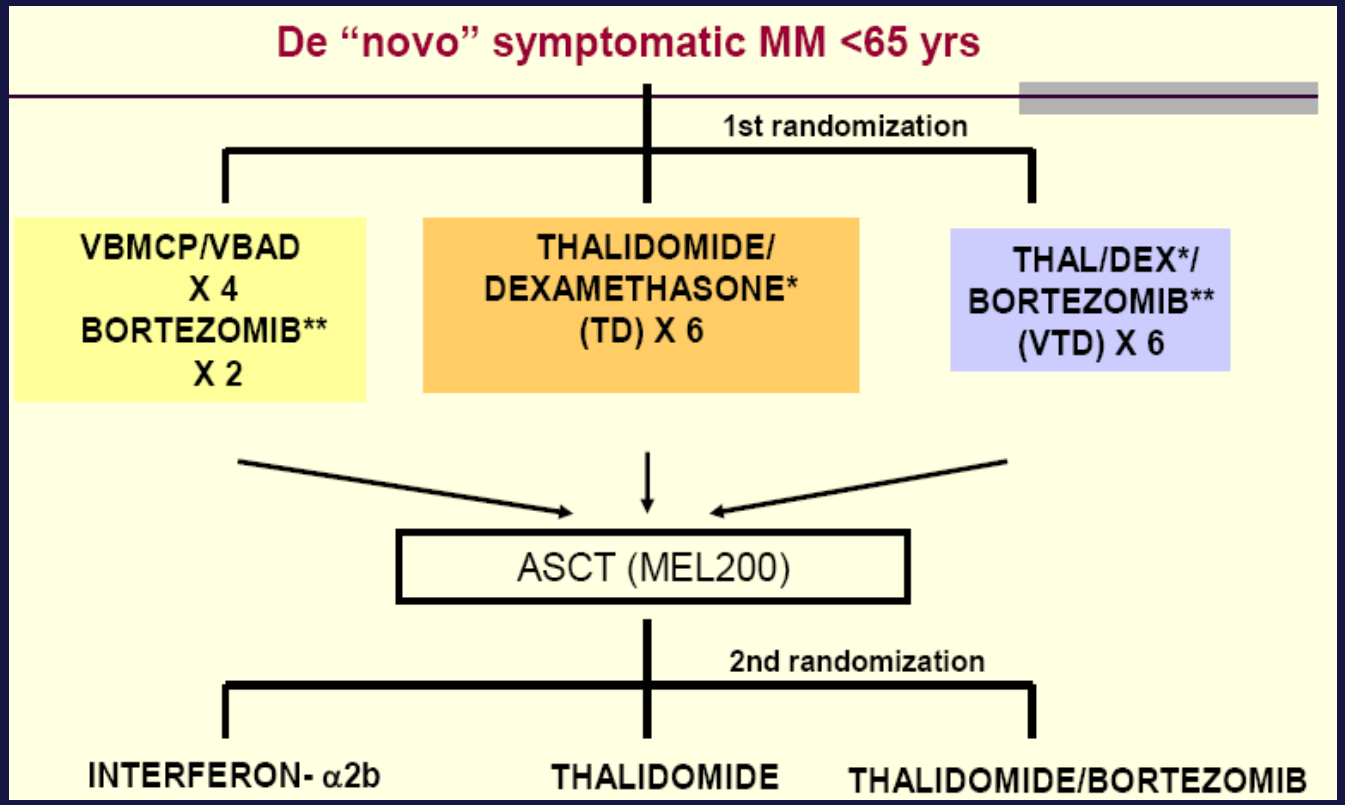
| Adverse events (AEs) | VAD (n=150) | PAD (n=150) |
|---|---|---|
| Any AEs | 82% | 87% |
| AEs grade 3/4 | 53% | 59% |
| AEs leading to discontinuation | 3% | 6% |
| Infections grade 2-4 | 42% | 54% |
| Herpes zoster | 2% | 15% (without prophylaxis)<br>9% (with prophylaxis) |
| Fatigue | 26% | 29% |
| Rash | 11% | 13% |
| PN grade 3/4 | 6% | 16% |

Sonneveld *et al.* EHA 2009 Abstract 473

# Phase III: VTD vs VBMCP/VBAD + V vs TD as induction

## Spanish Myeloma Group (PETHEMA/GEM) study

### Study design




Rosinol *et al*. ASH 2008 (abstract 654); IMW 2009 (abstract 160)

# Results

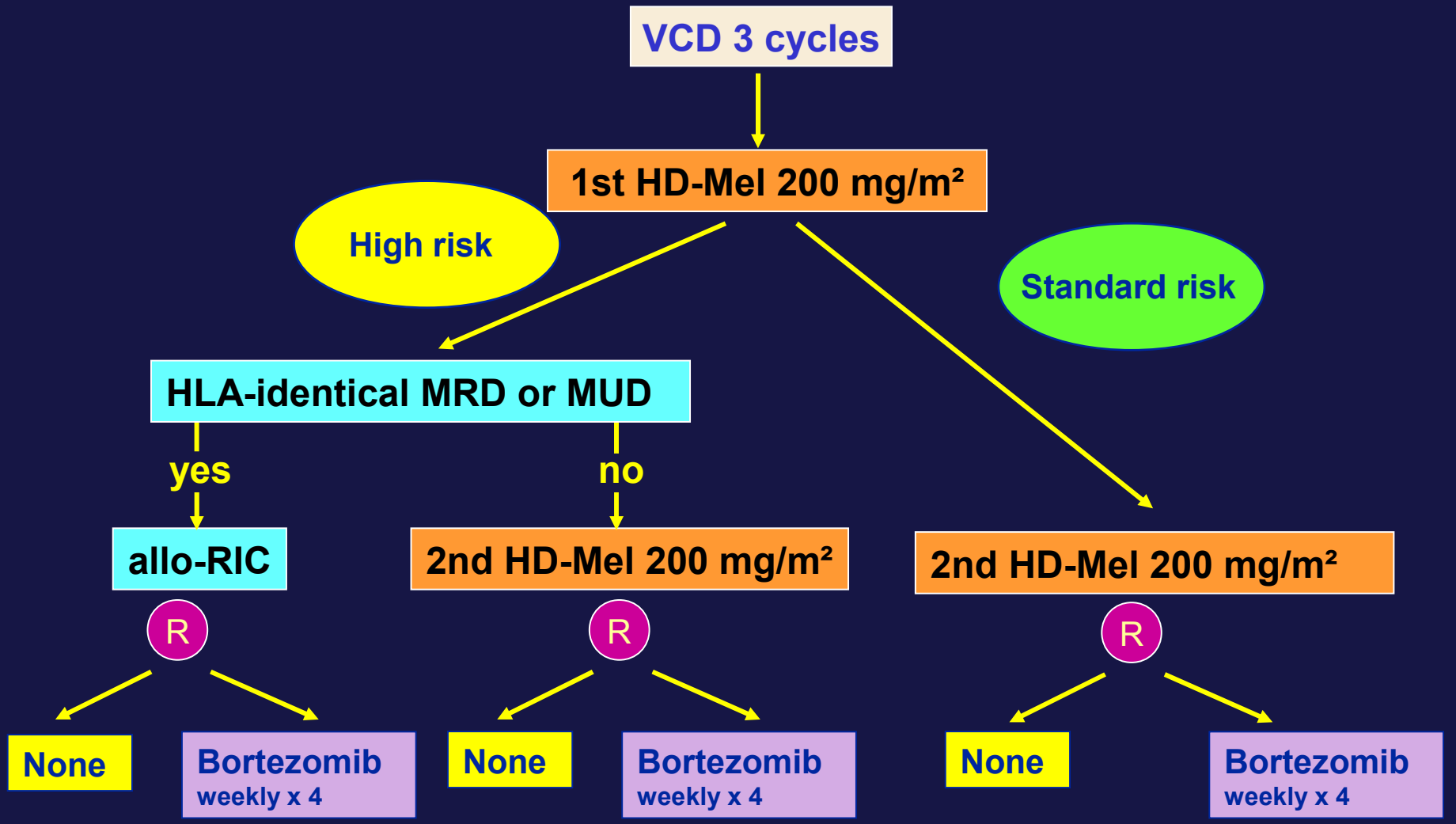
| | VTD (n=61) | VBCMP/VBAD + V (n=58) | TD (n=61) | *P* |
|---|---|---|---|---|
| **Response after induction** | | | | |
| CR | 30% | 20% | 6% | <0.01 |
| ≥ PR | 77% | 70% | 62% | NS |
| **Responses after ASCT** | | | | |
| CR | 48% | 43% | 23% | NS |

| | VTD | VBCMP/VBAD + V | TD |
|---|---|---|---|
| Grade 3/4 AEs | 54% | 50% | 38% |
| Specific events ≥ grade 3 | 16% PN | | 13% thrombotic events |

- VTD and VBCMP/VBAD + V result in higher CR rates than TD pre- and post-ASCT
- Toxicity in the three arms is not significantly different

Rosinol *et al*. ASH 2008 (abstract 654); IMW 2009 (abstract 160)

# DSMM XI Trial: VCD as induction regimen (bortezomib, cyclophosphamide, dexamethasone)




Knop *et al*. ASCO 2009: Abstract 8516

# Response data

## Interim Analysis:

**Response data on study day 63**

Interim analysis; investigator-based assessment (n = 200)

| | n (%) |
|---|---|
| ORR | 168 (84.0) |
| CR | 25 (12.5) |
| PR | 143 (71.5) |
| MR | 11 (5.5) |
| SD | 17 (8.5) |
| PD | 4 (2.0) |

Knop *et al*. ASCO 2009: Abstract 8516

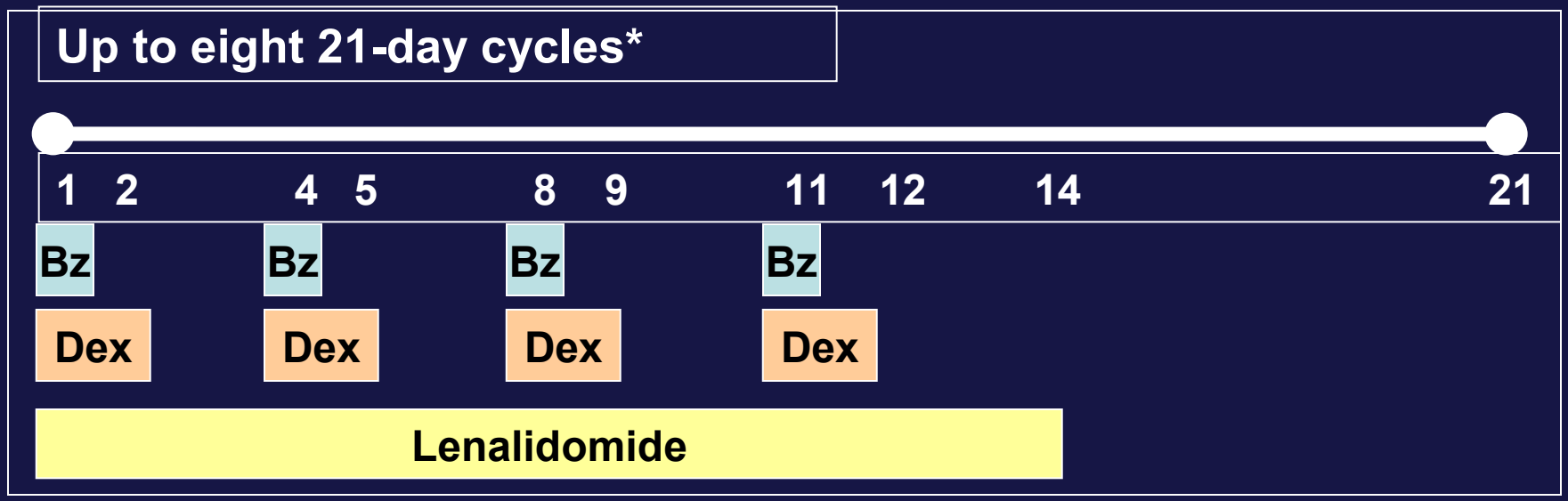
# Response according to cytogenetic subgroup

Responses (CR + PR) on study day 63 (investigator assessment)

| Molecular cytogenetics / FISH | CR + PR (%) | < PR (%) |
|---|---|---|
| Normal, n=51 | 86.3 | 13.7 |
| Abnormalities, n=91 | 82.4 | 17.6 |
| 13q-, n=55 | 81.8 | 18.2 |
| t(4;14), n=16 | 93.8 | 6.3 |
| 17p-, n=20 | 70 | 30 |
| Other, n=48 | 87.5 | 12.5 |
| Overall, n=200 | 84 | 16 |

Knop *et al*. ASCO 2009: Abstract 8516

# RVD Phase I/II in Newly Diagnosed MM: Study design




*Dex, 40 mg/day Days 1, 2, 4, 5, 8, 9, 11 and 12; 20 mg, cycles 5–8; Amended to 20 mg/10 mg cycles 1–4/5–8 based on safety data

- Pts ≥PR may proceed to ASCT after ≥4 cycles
- Maintenance therapy permitted in pts ≥SD using weekly (days 1 and 8) schedule of Bz, and Dex on days 1, 2, 8, and 9
- Antithrombotic therapy with daily aspirin (81 or 325 mg)

# Bortezomib consolidation

N=40
≥VGPR after ASCT

6 cycles with VTD, started within 6 months

6 patients converted to molecular remission

No clinical relapse at median follow-up of 26 months

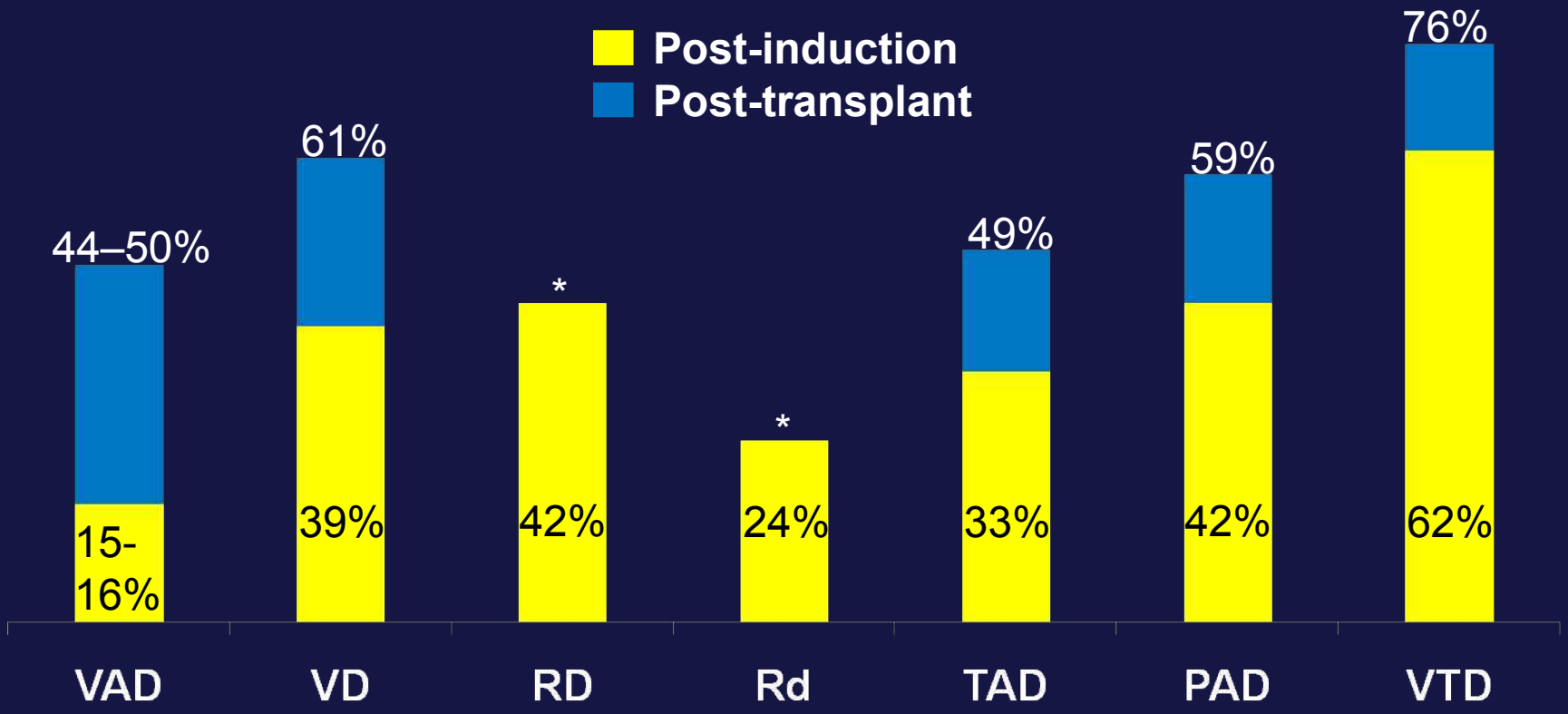
34 patients not achieving MR

8 relapses at median 12 months

Ladetto *et al*. ASH 2008 (abstract 3683)

# Summary of novel agent induction trials

## ≥VGPR rates post-induction and post-transplant




*Post-transplant data not available

Harousseau *et al*. ASH/ASCO symposium during ASH 2008
Rajkumar *et al*. ASCO 2008 (Abstract 8504);
ASH 2008 (joint ASH/ASCO symposium)

Lokhorst *et al*. *Haematologica* 2008;93:124–127
Sonneveld *et al*. ASH 2008 (Abstract 653); IMW (Abstract 152)
Cavo *et al*. ASH 2008 (Abstract 158); IMW 2009 (Abstract 451)

# Effect of Bortezomib on stem cell collection

# Novel agents and stem cell collection

## Thalidomide

- Adequate collection of stem cells[1]

## Lenalidomide

- **Cytotoxic effect on bone marrow[2]**
- **Evidence of decreased stem cell yield after lenalidomide exposure**
- **Recommendation: collection of PBSC within 6 months of initiation of lenalidomide[2,3]**
- **Mobilization with G-CSF + cyclophosphamide can overcome suppressive effect of lenalidomide treatment[4,5]**

## Bortezomib

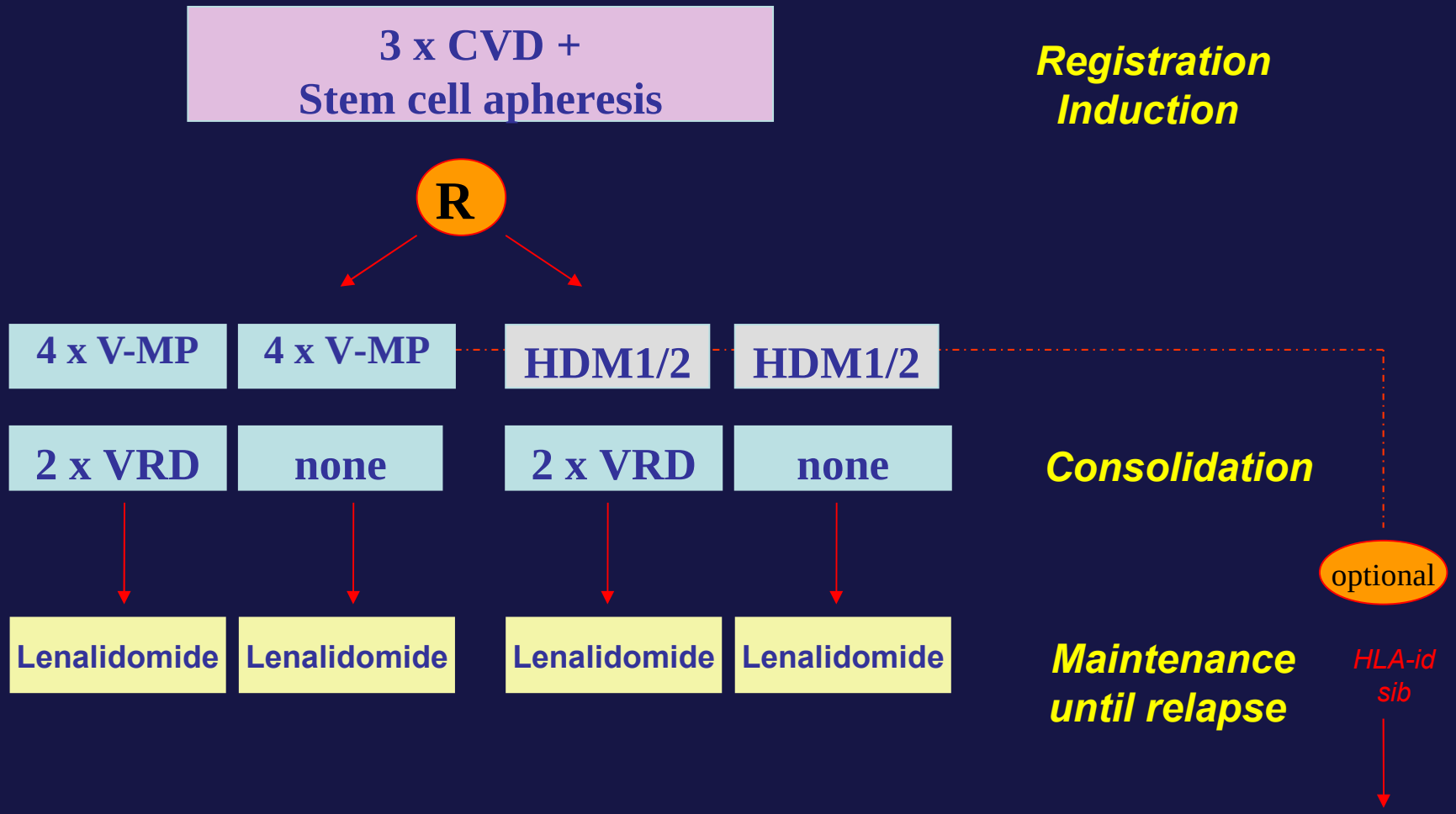
- **Not cytotoxic to bone marrow[6]**
- **Successful mobilization and adequate collection of PBSC with variety of induction regimens[7–10]**

PBSC, peripheral blood stem cells


1. Breitkreutz *et al*. *Leukemia* 2007;21:1294–1299
2. Kumar *et al*. *Leukemia* 2007;21:2035–2042
3. Mazumder *et al*. *Blood* 2007;110:(Abstract 3612)
4. Mark *et al*. Biol Blood Marrow Transplant 2008;14:795–798
5. Palumbo et al. EHA 2009 (Abstract 707)
6. San Miguel *et al*. *The Oncologist* 2006;11:51–61
7. Oakervee *et al*. *Br J Haematol* 2005;129:755–762
8. Harousseau *et al*. ASH 2008 (joint ASH/ASCO symposium)
9. Cavo *et al*. ASH 2008 (Abstract 158)
10. Goldschmidt *et al*. ASH 2008 (Abstract 3470)

# Novel agents alone *versus* intensive therapy + novel agents

## European Intergroup study




*Stem cell mobilisation after CVD in all patients*

# Part 1: Conclusions

- Including bortezomib in induction regimens improves overall and complete response rates pre- and post-transplant
  - Stem cell collection feasible

- Impact on overall survival with the novel induction regimens remains to be determined
  - To define optimal induction regimen: 2-drug vs 3 or 4-drug regimens

# Part 2
# Newly diagnosed MM patients not eligible for transplantation:

# Treatment of patients in the non-transplant setting

- Melphalan + prednisone (MP) has been considered standard treatment for patients not eligible for transplantation
  - Results are generally disappointing
- Novel agents are being incorporated into traditional regimens
  - Improvements in outcome seen (mainly in younger patients)
- Need to balance efficacy and toxicity to offer individualized treatment approach and improve survival
  - Consider age, physical condition, comorbidities

Reece. *Hematology (Am Soc Hematol Educ Program)* 2005:353–359
Kastritis *et al. Leukemia* 2009 [Epub]

# Summary of five MPT Phase III trials conducted in the upfront setting

| Regimen | n | CR+PR (%) | CR (%) | PFS/EFS/TTP | OS | Reference |
|---|---|---|---|---|---|---|
| Thal/MP vs MP | 129<br>126 | 76<br>48 | 16<br>4 | 21.8 m<br>14.5 m | 45 m<br>47.6 m | Palumbo *et al*. *Blood* 2008; 112:3107–3114 |
| Thal/MP vs MP | 191<br>124 | 76<br>35 | 13<br>2 | 27.5 m<br>17.8 m | 51.6 m*<br>33.2 m | Facon, *et al*. *Lancet* 2007; 370:1209–1218 |
| Thal/MP vs MP (>75 y) | 113<br>116 | 62<br>31 | 7<br>1 | 24.1 m<br>18.5 m | 44 m*<br>29.1 m | Hulin, *et al*. *JCO* 2009 [Epub] |
| Thal/MP* vs MP | 363 | 42<br>28 | 6†<br>3† | 20 m<br>18 m | 29 m<br>33 m | Gulbrandsen et al. EHA 2008 (Abstract 209) |
| Thal/MP vs MP | 152<br>149 | 66<br>47 | 2<br>2 | EFS 13 m vs 9 m<br>PFS 14 m vs 10 m | 40 m*<br>30 m | Wijermans *et al*. IMW 2009 (Abstract 116) |

*Thal doses: 200–400 mg

†CR + nCR

**In 5/5 studies, MPT was superior to MP in terms of PFS and/or TTP.**
***In 3/5 studies, MPT was superior to MP in terms of OS.**

# 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 patients with symptomatic MM who were not candidates for HDT-ASCT due to age (≥65 yrs) or co-morbid conditions
- Stratification: $\beta_2$-microglobulin, albumin, region

RANDOMIZE

**VMP**

Cycles 1–4
Bortezomib 1.3 mg/m$^2$ IV: d 1,4,8,11,22,25,29,32
Melphalan 9 mg/m$^2$ and prednisone 60 mg/m$^2$: d 1–4

Cycles 5–9
Bortezomib 1.3 mg/m$^2$ IV: d 1,8,22,29
Melphalan 9 mg/m$^2$ and prednisone 60 mg/m$^2$: d 1–4

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

**MP**

Cycles 1–9
Melphalan 9 mg/m$^2$ and prednisone 60 mg/m$^2$: d 1–4

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

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

# VISTA: Response data

## Responses according to EBMT criteria[1]

| | VMP n=337 | MP n=331 | p-value |
|---|---|---|---|
| ORR (≥PR) | 71% | 35% | $<10^{-6}$ |
| CR | 30% | 4% | $<10^{-6}$ |
| PR | 40% | 31% | |
| MR | 9% | 22% | |
| SD | 18% | 40% | |

## Time to response and duration of response

| | VMP | MP | p-value |
|---|---|---|---|
| **Median time to response, months** | | | |
| Time to first response* | 1.4 | 4.2 | $<10^{-10}$ |
| Time to CR* | 4.2 | 5.3 | $<10^{-10}$ |
| **Median DOR, months** | | | |
| All responders | 19.9 | 13.1 | |
| Patients achieving CR | 24.0 | 12.8 | |

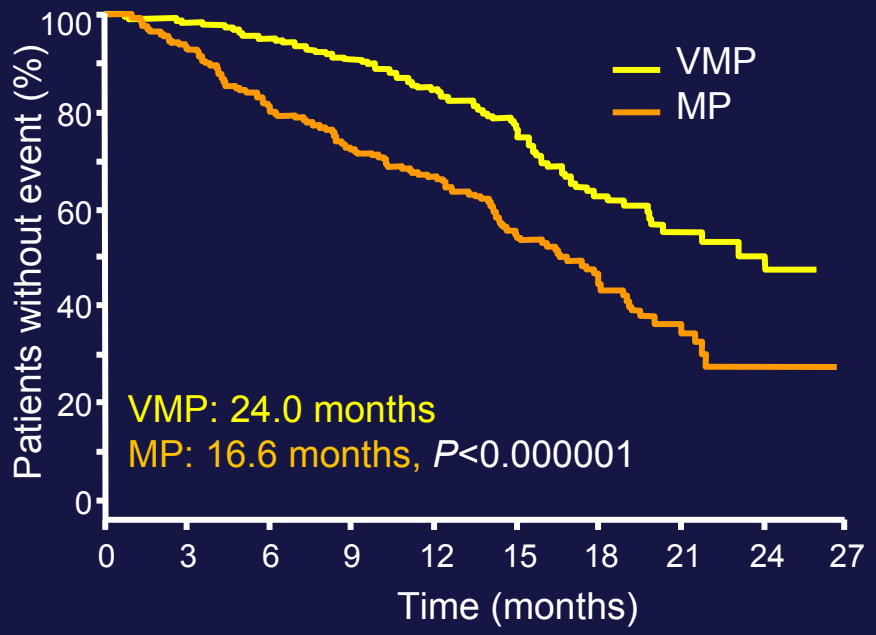
*Medians shown for responding patients; p-values based on total study population

1. Bladé et al. Br J Haematol 1998;102:1115-23.

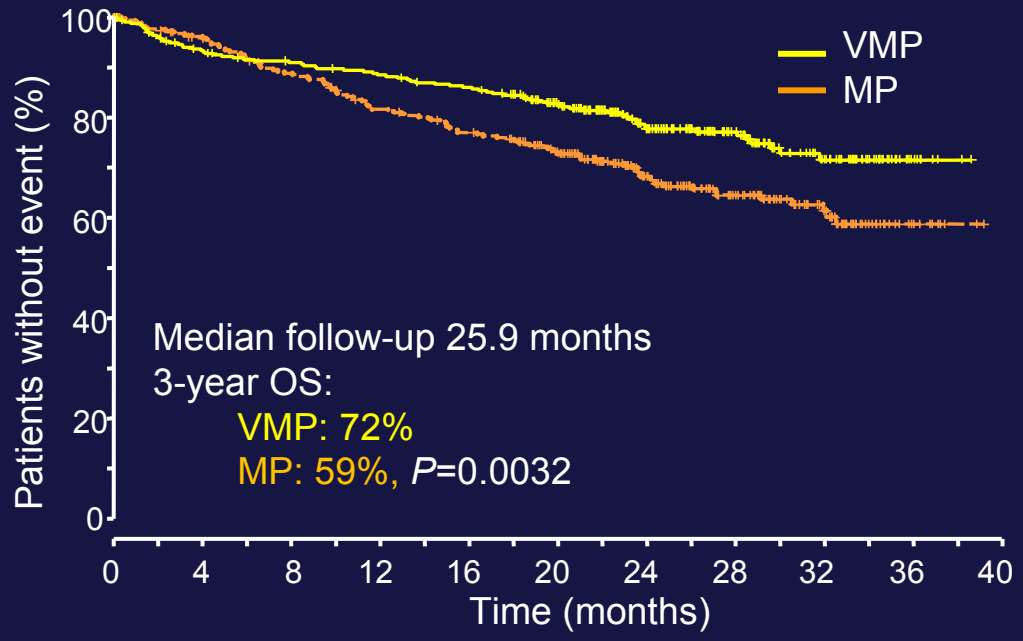
San Miguel *et al. N Engl J Med* 2008;359:906–17

# Phase III VISTA: VMP vs MP
## Efficacy

### Time to progression
**52% reduced risk of progression on VMP**




### Overall survival
**~36% reduced risk of death on VMP**




- ***43% of MP patients received bortezomib upon progression***
- **Analysis bortezomib >4 cycles: OS at 1 and 2 years: 98.5% and 89%**
- **Treatment-related death: 2% in both arms**

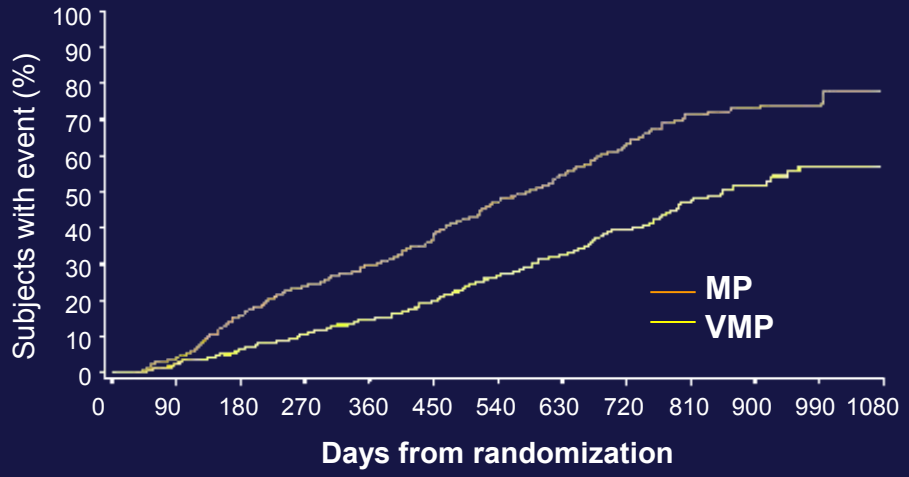
San Miguel *et al*. *N Engl J Med* 2008;359:906–917

San Miguel *et al*. ASH 2008 (abstract 650)

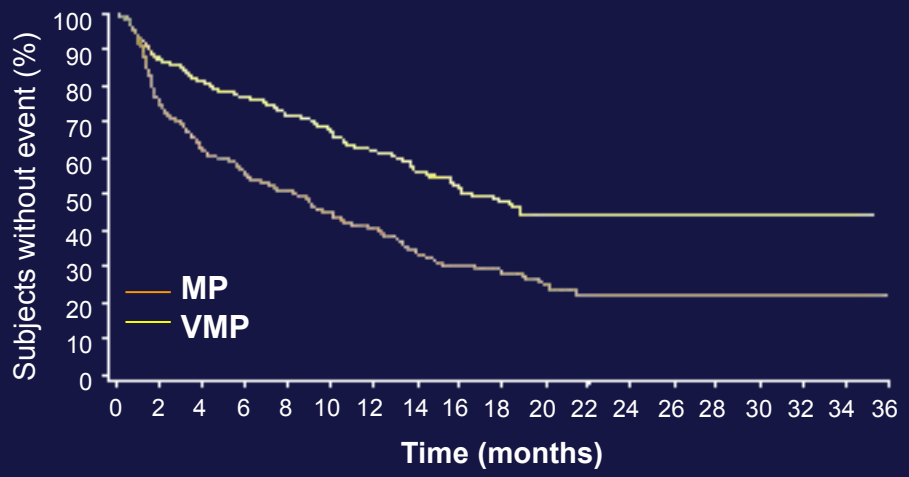
# VISTA: time to next therapy (TNT) and treatment-free interval (TFI)

**Median TNT and TFI significantly longer for VMP versus MP:**

**TNT** 28.1 vs 19.2 months
(HR 0.53, *P*<0.000001)




**TFI** 16.6 vs 8.4 months
(HR 0.54, *P*<0.000001)




**Fewer patients in VMP versus MP arm required subsequent therapy (38% vs 57%)**

San Miguel *et al*. ASH 2008 (abstract 650)

# VISTA: adverse events

| | VMP (n=340) | | MP (n=337) | |
|---|---|---|---|---|
| AE, % | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| Neutropenia | 29 | 11 | 23 | 15 |
| Thrombocytopenia | 20 | 18 | 16 | 15 |
| Anemia | 16 | 3 | 20 | 8 |
| GI | 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 more frequent with VMP (14% vs 4%)
  - Rate with VMP 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

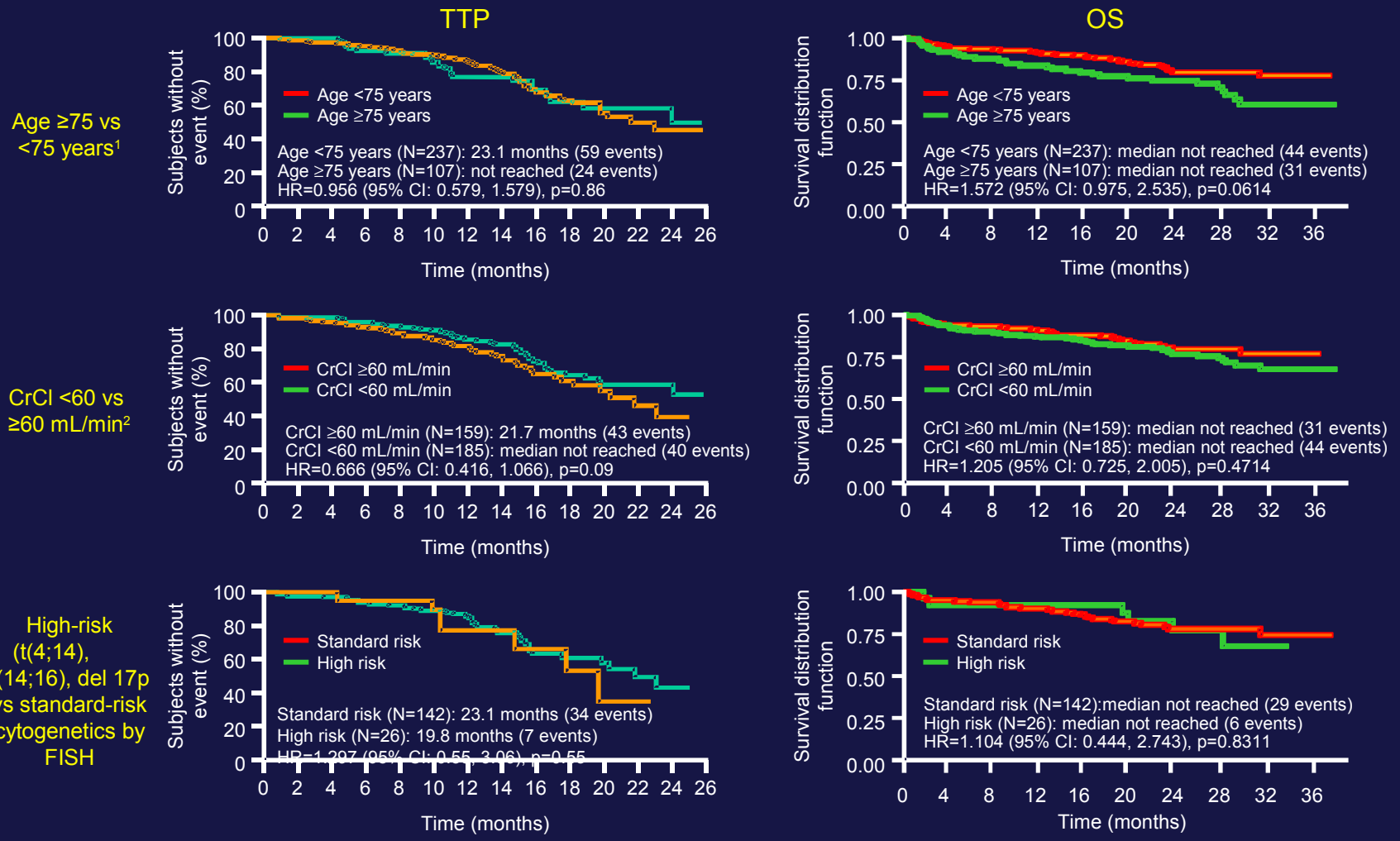
San Miguel *et al*. ASH 2008 (abstract 650)

# Subgroup analysis

- Treatment effect of VMP over MP consistently maintained across all tested subgroups for TTP, OS and response:
  - Age (<75, ≥75)
  - ISS Stage (I,II,III)
  - Cytogenetics (Standard Risk, High Risk)
  - Renal Function (CrCl<60ml/min, CrCl≥60ml/min)

San Miguel et al. N Engl J Med 2008; 359: 906-917

# VMP: subgroup analysis in patients with poor prognostic characteristics




San Miguel et al. Blood 2008; 112: Abstract 650

# VISTA subgroup analysis: efficacy in patients ≥75 vs <75 years

| | Age ≥ 75 years | | | Ages < 75 years | | |
|---|---|---|---|---|---|---|
| | VMP | MP | *P* | VMP | MP | *P* |
| CR + PR | 60% | 40% | 0.0047 | 75% | 32% | <0.00001 |
| CR | 26% | 3% | <0.0001 | 32% | 4% | <0.00001 |
| TTP | Median not reached | 16.4 months | 0.018 | 23.1 months | 17.4 months | 0.00001 |
| 2-year OS | 74% | 58% | 0.19 | 79% | 73% | 0.014 |
| 3-year OS | 60% | 44% | 0.19 | 77% | 65% | 0.014 |

**Rates of serious AEs were higher in patients ≥ 75 years in both the VMP and MP arms, indicating an effect independent of the addition of bortezomib**

Kropff *et al*. IMW 2009 (abstract 84)

# Subsequent therapy

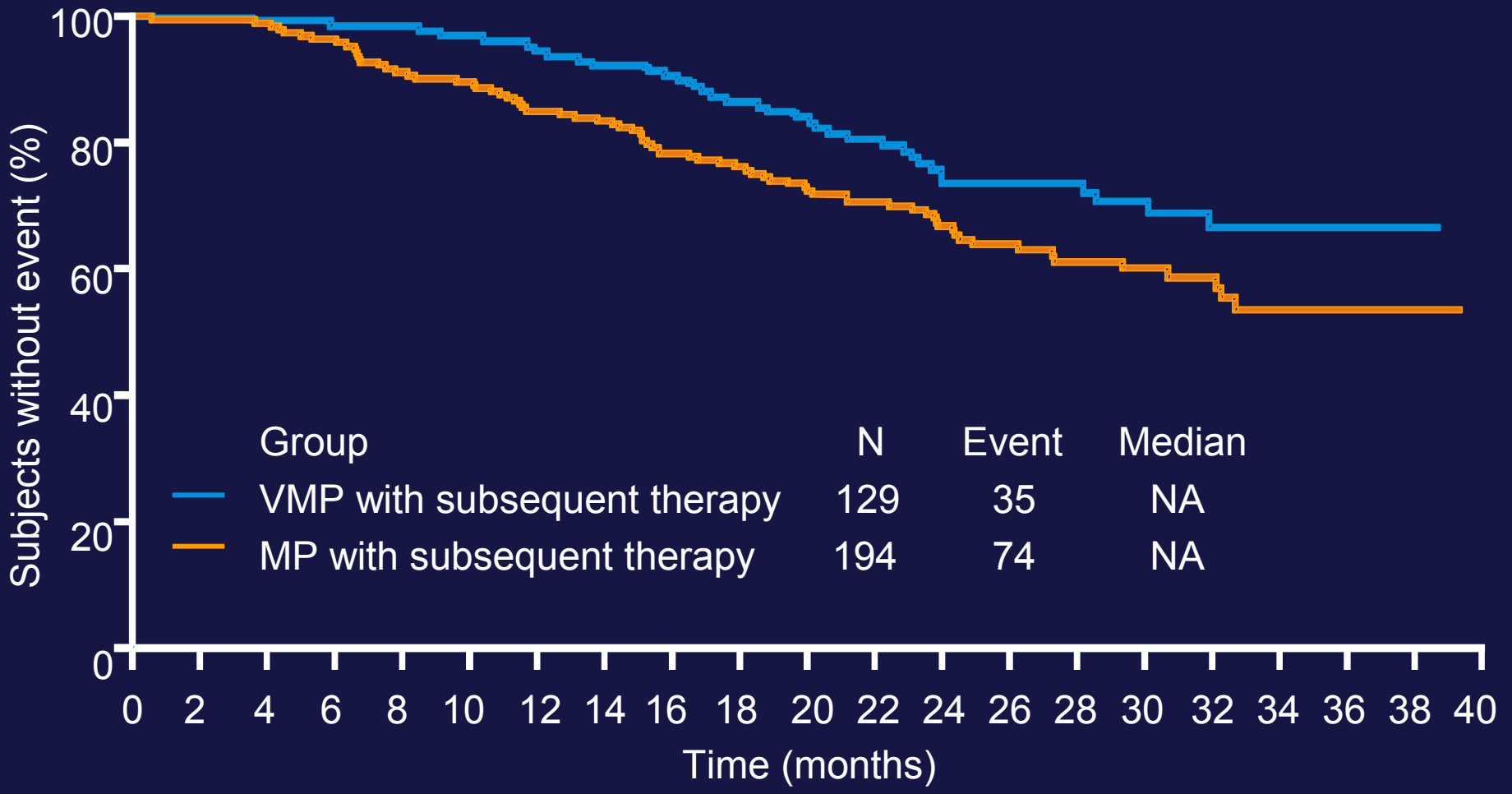
- **Fewer patients in the VMP versus MP arm (38% vs 57%, respectively) had required subsequent therapy by the time of data cut-off**

| | VMP (n=129) | MP (n=194) |
|---|---|---|
| Bortezomib | 21 (18%) | 84 (43%) |
| Thalidomide | 63 (49%) | 86 (44%) |
| Lenalidomide | 25 (19%) | 12 (6%) |
| Others | 20 (16%) | 12 (6%) |

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

San Miguel et al. Blood 2008; 112: Abstract 650

# VMP plus subsequent therapy vs. MP patients plus subsequent therapy, ITT Landmark analysis




San Miguel et al. Blood 2008; 112: Abstract 650

# VISTA subgroup analysis: influence of renal impairment

- VMP more effective than MP in patients with renal impairment

| | VMP | MP |
|---|---|---|
| ORR | 70% | 43% |
| CR | 28% | 4% |
| Time to first response (median) | 1.4 months | 3.5 months |
| Duration of response (median) | 19.9 months | 13.1 months |
| TTP<br>Any renal impairment<br>Severe renal impairment (CrCl ≤ 30 mL/min) | <br>median not reached<br>19.8 months | <br>16.1 months<br>14.5 months |
| Reversal or renal impairment (improvement in CrCl from <50 mL/min at baseline to >60 mL/min on treatment) | 44% | 34% |

- Median time to reversal significantly shorter with VMP vs MP (*P*=0.03)
- Safety profiles comparable among patients with CrCl 31–60 and >60 mL/min for VMP and MP

Dimopoulos *et al*. ASH 2008 (abstract 1727)

# Reversal of Renal Impairment

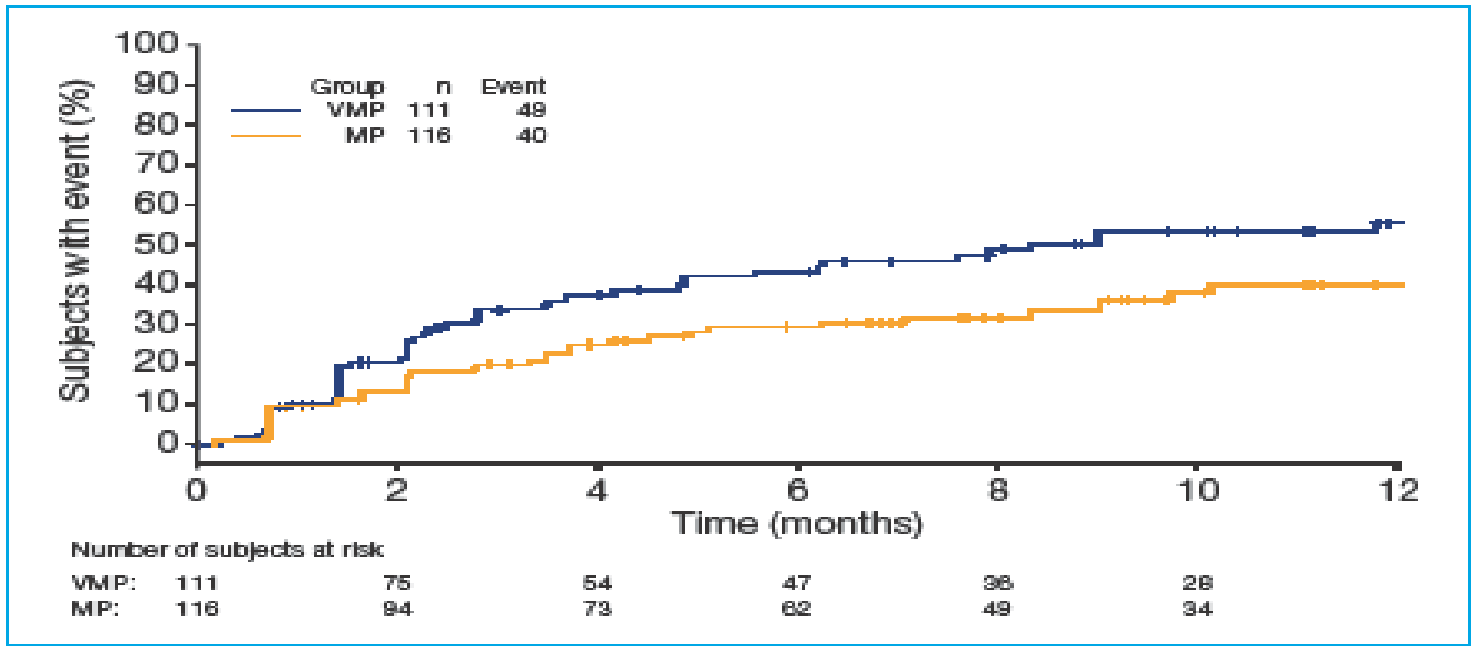
- The rate of renal impairment reversal was more pronounced with VMP
- The rate of $CR^{renal}$ was higher with VMP vs.MP

| | VMP | MP |
|---|---|---|
| **Rate of reversal of renal failure** (Baseline CrCl <50 improving to ≥ 60mL/min on treatment) | | |
| All Patients CrCl <50mL/min | 44% | 34% |
| CrCl 30 - <50mL/min | 46% | 39% |
| CrCL <30mL/min | 37% | 7% |
| CrCl increases ≥20mL/min | 86% | 63% |
| **Renal Responses** | | |
| $CR^{renal}$ | 44% | 34% |
| $PR^{renal}$ | - | 50% |
| $MR^{renal}$ | 42% | 67% |

Dimopoulos et al. Blood 2008; 112: Abstract 1727

# Time to Reversal of Renal Impairment

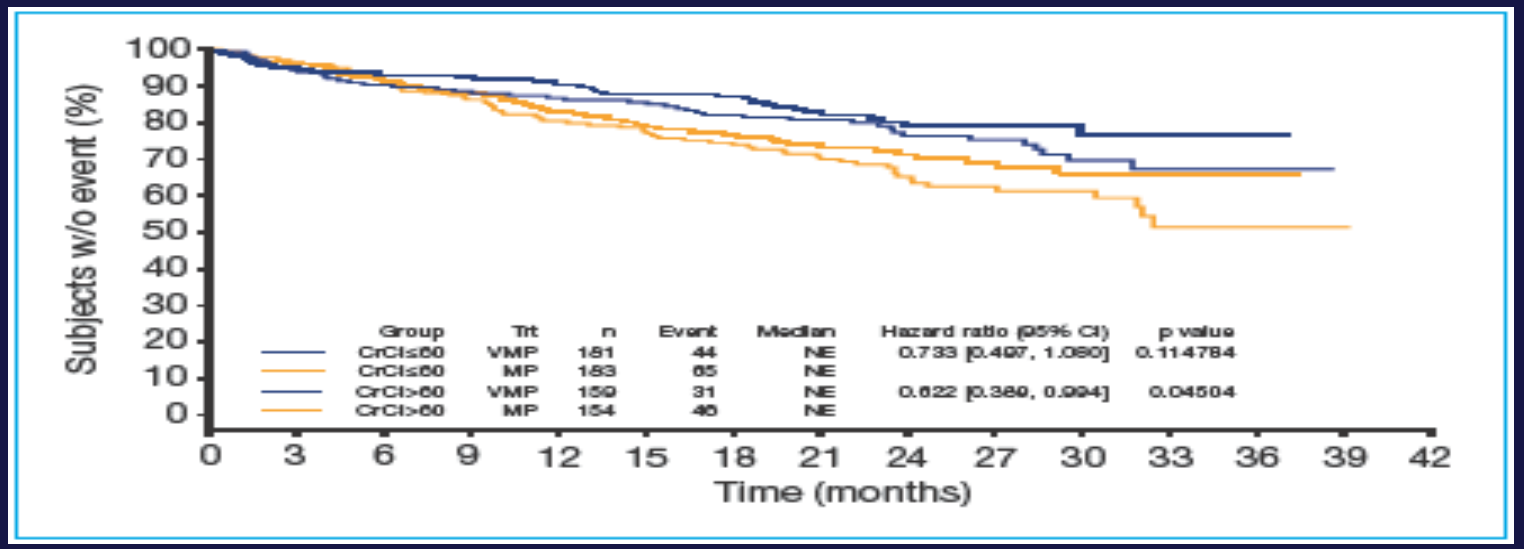
- Median time to renal impairment reversal in all patients with baseline CrCl <50 mL/min significantly shorter with VMP vs MP
  - 9.0 months (VMP) vs 13.6 months (MP) for all patients with baseline CrCl <50 mL/min




Dimopoulos et al. Blood 2008; 112: Abstract 1727

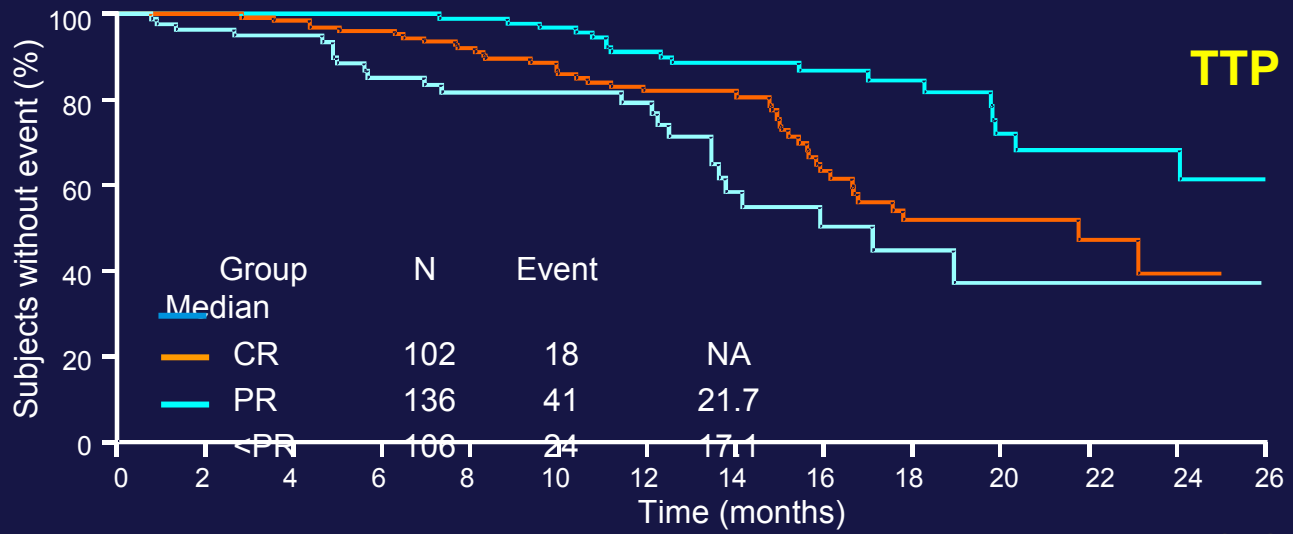
# Overall survival

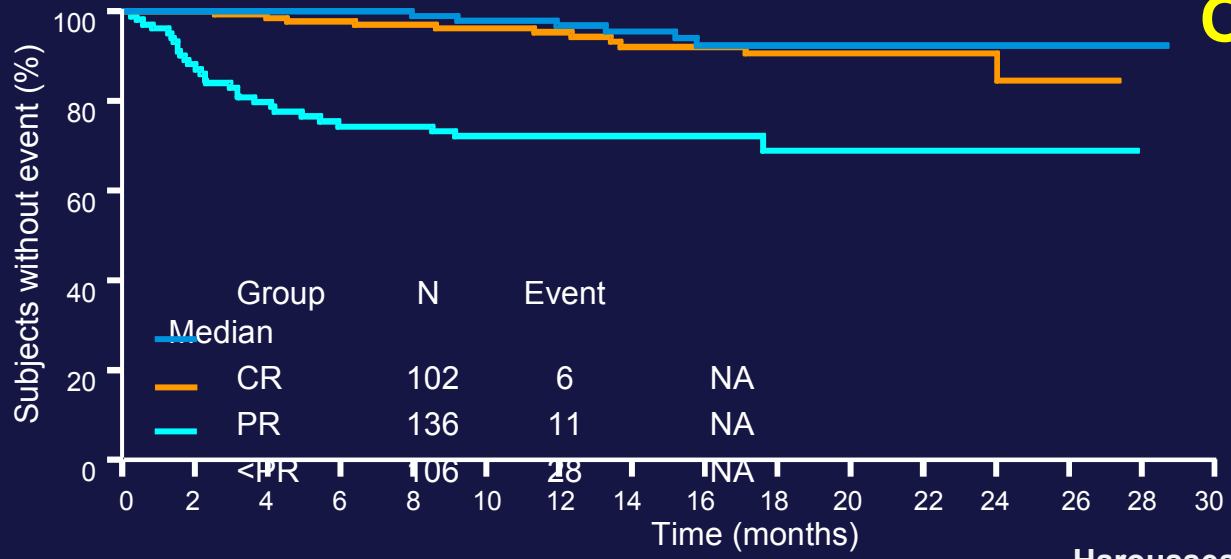
- OS consistently longer with VMP vs.MP in patients with:
  - Any renal impairment (3-year OS: 67.4% vs 51.5%, *P*=0.1148)
  - Normal renal function (3-year OS: 76.8% vs 66.2%, *P*=0.045)
- OS also longer with VMP versus MP in small cohort of patients with severe renal impairment (CrCl ≤30 mL/min):
  - Median OS 28.7 vs 24.7 months, *P*=0.4687
- OS appeared similar between patients with renal impairment and those with normal renal function with both VMP and MP




Dimopoulos et al. Blood 2008; 112: Abstract 1727

# VISTA: TTP and OS in patients achieving CR vs PR vs <PR with VMP




- CR associated with significantly longer TTP vs. PR (HR 0.45, p=0.004)
- Significant benefit also seen for CR+PR vs .<PR

- No significant difference in OS with CR vs. PR, likely due to the small number of deaths (HR 0.59, p=0.26)
- Significant benefit seen for CR+PR vs. <PR

Harousseau et al. Blood 2008; 112: Abstract 2778

# Treatment Emergent PN

| | All | Grade ≥3 | Discontinued VMP | Selectively Discontinued bortezomib* | Dose Reduced |
|---|---|---|---|---|---|
| PN NEC** | 47% | 13% | 3% | 11% | 22% |
| Neuropathy Peripheral | 3% | 0 | 0 | <1% | 1% |
| Motor PN | 6% | 2% | 0 | 1% | 2% |
| Sensory PN | 44% | 13% | 3% | 11% | 21% |

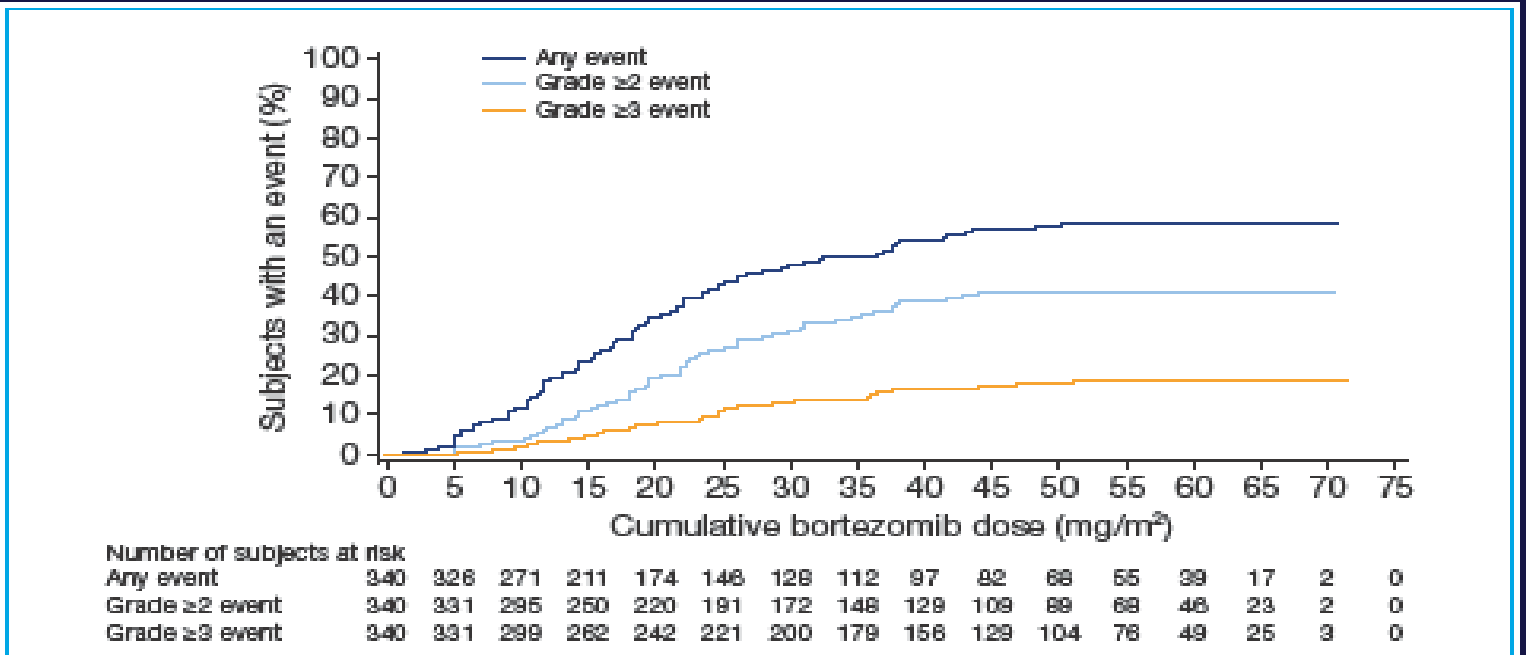
* Continued to receive melphalan plus prednisone but discontinued bortezomib;
** PN NEC – MedDRA higher level term, including the three preferred terms shown; some patients reported events in more than one of the preferred terms
NEC – Not elsewhere classified

- **Median time to onset of PN 3.3 months (range 0.6–12.4)**
- **History of neuropathy appeared the only consistent strong risk factor for any PN (*P*=0.0065), and for grade ≥2 (*P*=0.0032) and grade ≥3 PN (*P*=0.023).**

**Mateos et al. Clin Lymph Myeloma 2009; Abstract 172**

# Cumulative Dose to First Onset of PN

- The median cumulative bortezomib dose to the first onset of any grade of PN event was 32.6 mg/m$^2$
  - PN rate reached a plateau at a cumulative bortezomib dose of approximately 45 mg/m$^2$




| Number of subjects at risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Any event | 340 | 326 | 271 | 211 | 174 | 146 | 128 | 112 | 97 | 82 | 68 | 55 | 39 | 17 | 2 | 0 |
| Grade ≥2 event | 340 | 331 | 295 | 250 | 220 | 191 | 172 | 148 | 129 | 109 | 89 | 68 | 46 | 23 | 2 | 0 |
| Grade ≥3 event | 340 | 331 | 299 | 262 | 242 | 221 | 200 | 179 | 156 | 129 | 104 | 76 | 49 | 25 | 3 | 0 |

Mateos et al. Clin Lymph Myeloma 2009; Abstract 172

# PN Reversibility

- 79% of PN events had improved by at least one NCI CTCAE grade in a median of 1.9 months
- 60% of events had completely resolved in a median of 5.7 months
- With longer follow-up, more patients achieved complete resolution of their PN symptoms

## Conclusions

- VMP-associated PN resolved in the majority of cases
- Pre-existing neuropathy appeared to be the only consistent baseline risk factor
- Most patients who developed PN benefited from therapy

Mateos et al. Clin Lymph Myeloma 2009; Abstract 172

# Phase II study: PAD induction + reduced-intensity ASCT + lenalidomide consolidation/maintenance in elderly patients with newly diagnosed MM

- Patients (n=102)
  - aged 65–75 years

- Treatment

**Induction (four 21-day PAD cycles)**
**Bortezomib 1.3 mg/m$^2$ days 1, 4, 8, 11**
**Pegylated-lyposomal-doxorubicin 30 mg/m$^2$ day 4**
**Dex 40 mg days 1-4, 8-11, 15-18**

**Intensification**
**Tandem Melphalan 100 mg/m$^2$ (MEL100) + ASCT**

**Consolidation (four 28-day LP cycles)**
**Lenalidomide 25 mg days 1-21 +**
**Prednisone 50 mg every other day**

**Maintenance**
**Lenalidomide 10 mg days 1-21 every 28 days until relapse**

**Palumbo *et al*. EHA 2009: Abstract 497**

# Results

## Most frequent grade 3/4 adverse events

**During PAD:**

- thrombocytopenia (17%)
- neutropenia (10%)
- peripheral neuropathy (16%)
- Pneumonia (10%)

**During LP consolidation and L maintenance:**

- neutropenia (17%)
- thrombocytopenia (6%)
- Cutaneous rash (4%)

**Conclusion**

•Bortezomib as induction before transplantation, followed by lenalidomide as consolidation-maintenance induced a very high response rate and prolonged 3-year PFS

Palumbo *et al*. EHA 2009: Abstract 497

# Results

| | After PAD | After tandem MEL100 + ASCT | After LP Consolidation and L maintenance |
|---|---|---|---|
| CR | 13% | 39% | 66% |
| ≥ VGPR | 59% | 82% | 86% |

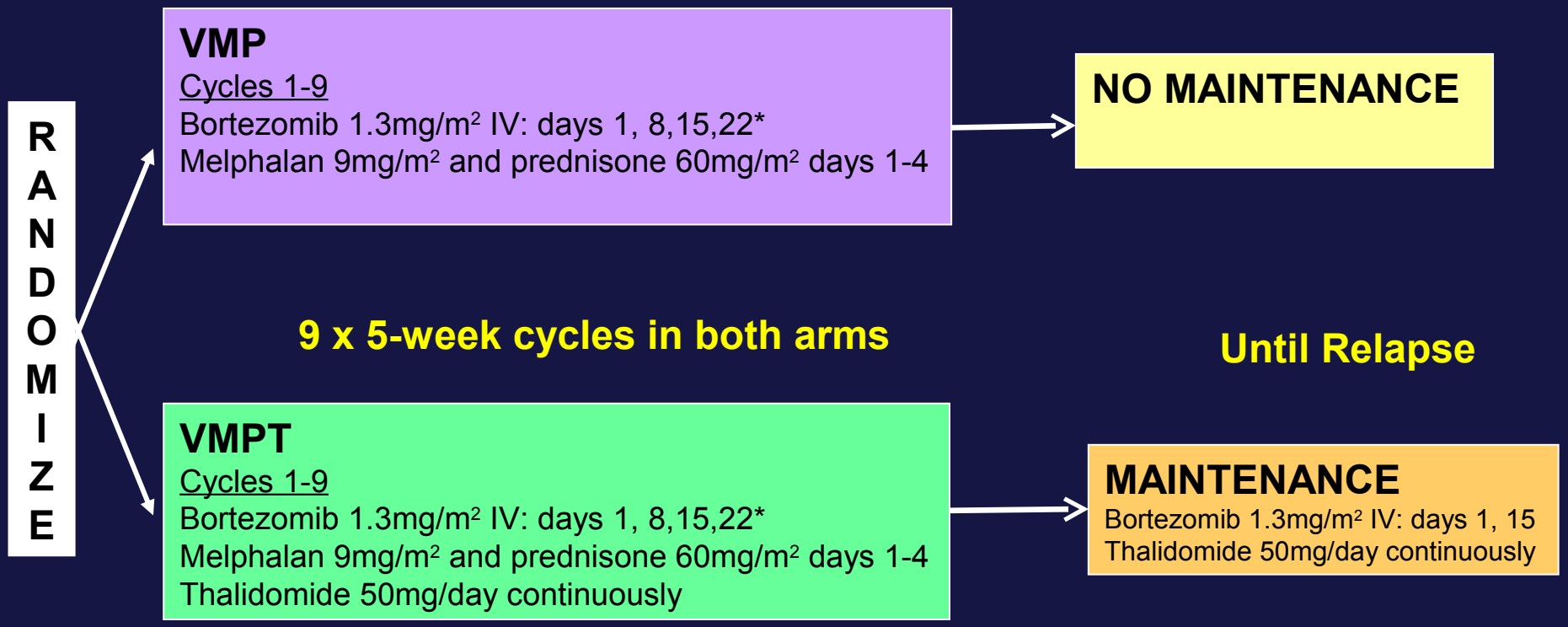
- Median follow-up: 20.3 months
  - 3-year PFS 68.8%
  - 3-year TTP 74.7%
  - 3-year OS 86.3%

- Similar TTP in patients with high risk cytogenetic profile, including del17 or t(4;14) or t(14;16), and those with standard cytogenetic profile

Palumbo *et al*. EHA 2009: Abstract 497

# GIMEMA Study Design

- 511 Patients (≥ 65 years) randomized from 58 Italian Centres
- Protocol amended to change bortezomib from biweekly to weekly infusions




*** 64 VMP patients and 71 VMPT patients were treated with twice-weekly infusions of bortezomib**

Palumbo *et al*. EHA 2009: Abstract 472

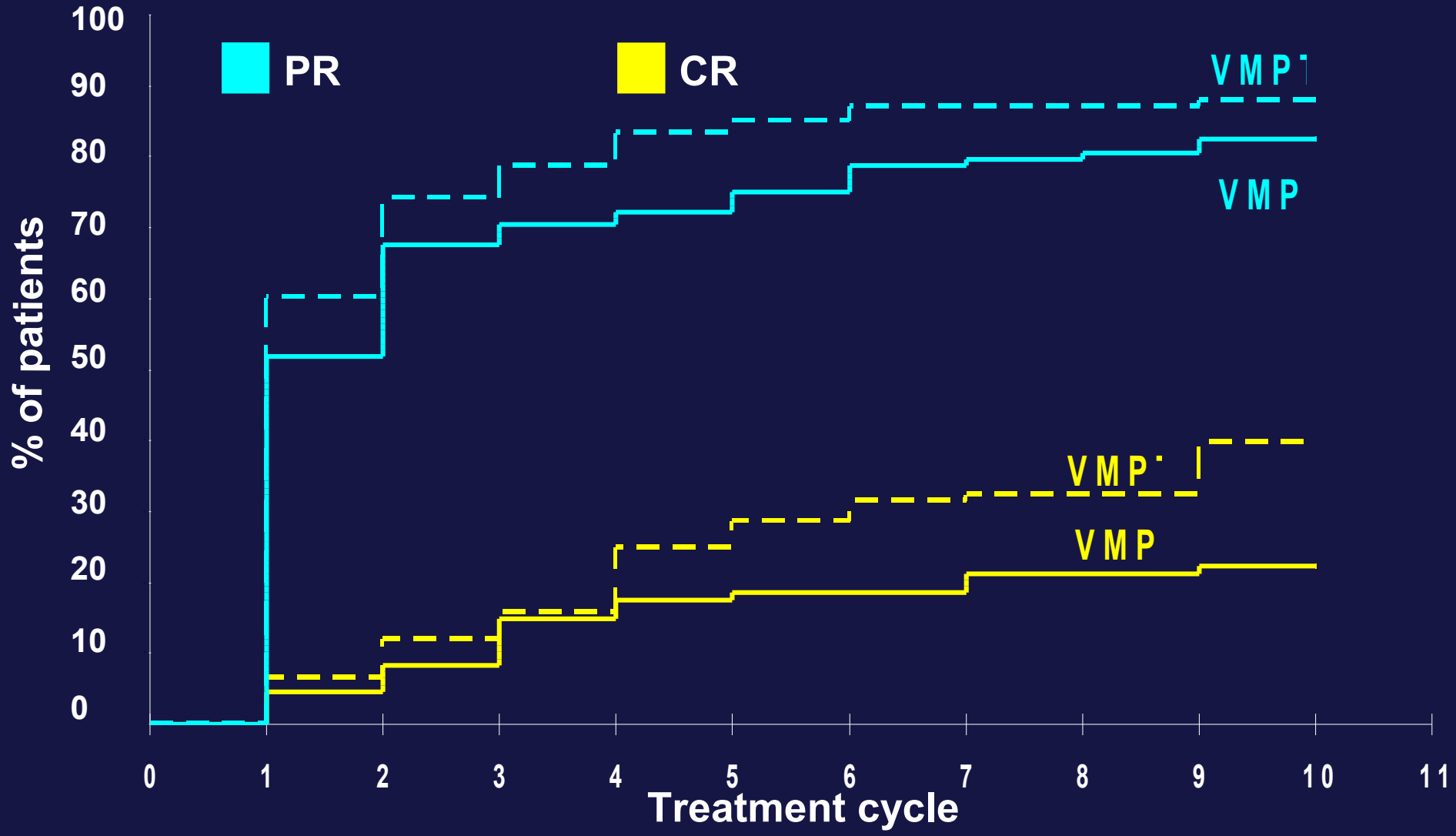
# Best Response

- Median number of cycles in each treatment arm: 5

| | VMPT group (n=221) | VMP group (n=229) | *P* |
|---|---|---|---|
| ORR | 84% | 78% | - |
| CR | 35% | 21% | < 0.0001 |
| VGPR | 16% | 21% | - |
| ≥ VGPR | 51% | 42% | 0.06 |
| PR | 33% | 36% | - |
| SD | 9% | 18% | - |
| PD | 1% | 1% | - |

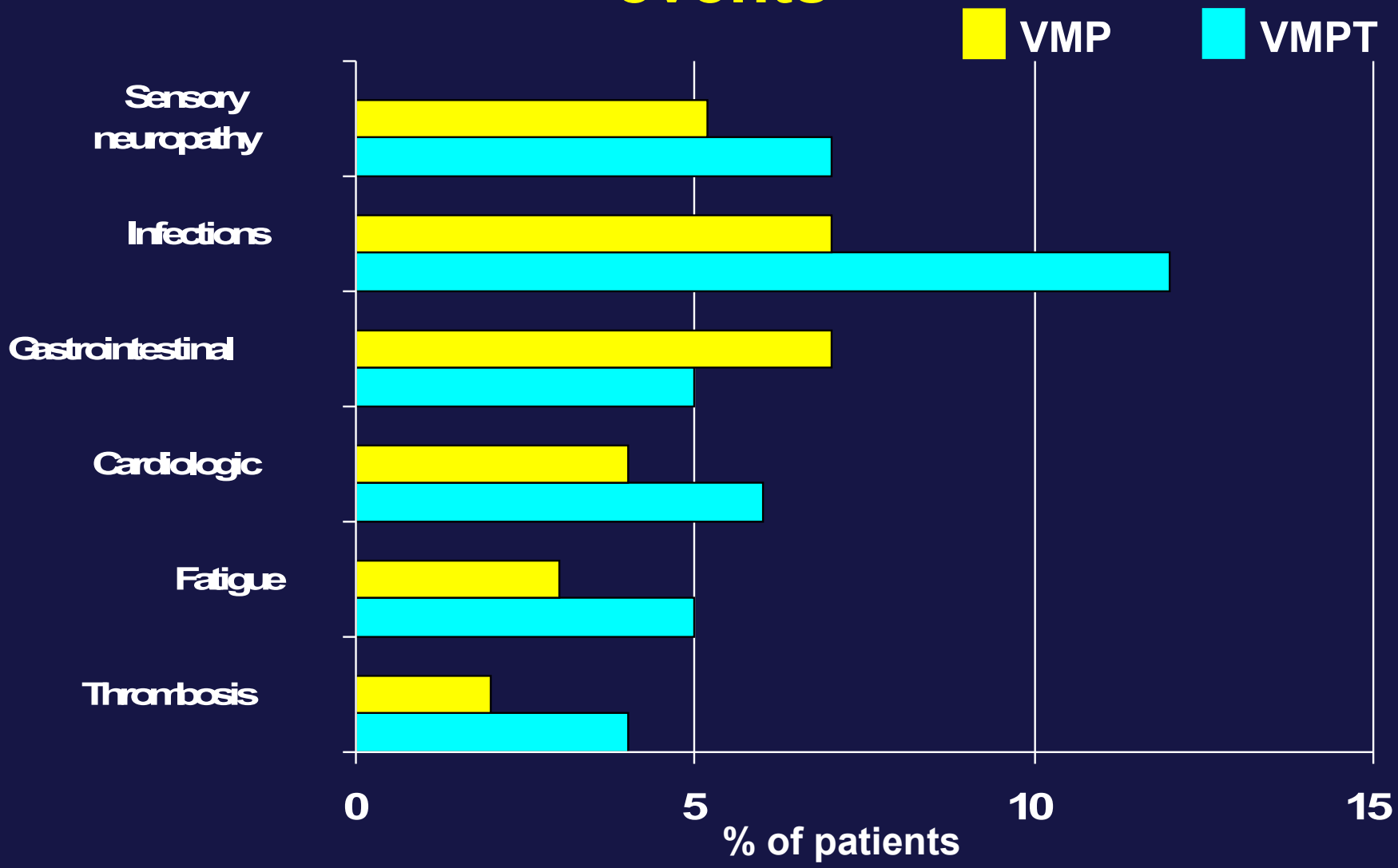
Palumbo *et al*. EHA 2009: Abstract 472

# Time to response




Palumbo *et al*. EHA 2009: Abstract 472

# Grade 3-4 non-hematological adverse events




Palumbo *et al*. EHA 2009: Abstract 472

# Efficacy and toxicity

## Bortezomib twice-weekly versus bortezomib once-weekly infusion

| | VMPT | | VMP | |
|---|---|---|---|---|
| | twice weekly (n=71) | weekly (n=150) | twice weekly (n=64) | weekly (n=165) |
| CR | 38% | 32% | 27% | 20% |
| Grade 3-4 Peripheral neuropathy | 18% | 2% | 14% | 2% |
| Dose reduction* | 42% | 11% | 35% | 13% |
| Discontinuation* | 10% | 3% | 15% | 4% |

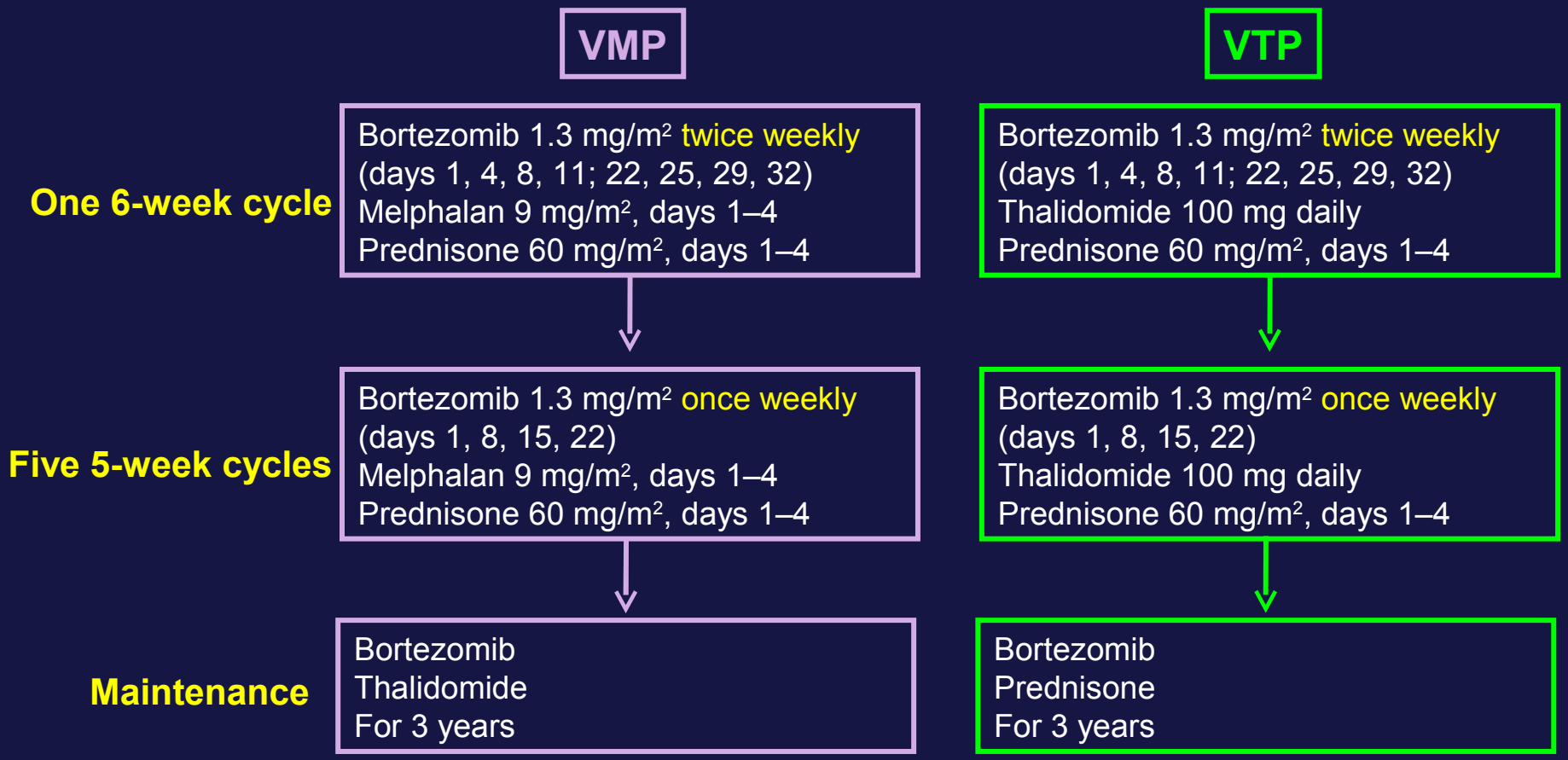
*Due to peripheral neuropathy

25 VMPT and 19 VMP patients received both twice- and once-weekly bortezomib

Palumbo *et al*. EHA 2009: Abstract 472

# PETHEMA: Study Design

- **Patients:** n=260, >65 years old
- **Treatment :** maximum of 6 cycles (31 weeks)




Mateos *et al*. EHA 2009: Abstract 471

# Treatment of very elderly / frail patients

# Treatment of very elderly/frail patients no trial data

- 30% of patients in VISTA were ≥75 years old
  - VMP highly effective in this population
  - Safety profile generally comparable, except for a bortezomib-independent higher rate of serious AEs in elderly patients

- Italian and Spanish studies with reduced frequency of administration of bortezomib
  - Significant efficacy is maintained plus reduction in toxicity, in particular significant reduction in PN

- Challenge: balancing efficacy and toxicity
  - Dose modifications to optimize duration of treatment

# Recommended adjusted therapy

| Autologous transplantation | Full dose chemotherapy | Reduced dose chemotherapy |
|---|---|---|
| <65 years | 65-75 years | >75 years |
| In good clinical condition normal:<br>•Cardiac<br>•Pulmonary<br>•Liver<br>•Renal function | In good clinical condition normal:<br>•Cardiac<br>•Pulmonary<br>•Liver<br>•Renal function | In good clinical condition normal:<br>•Cardiac<br>•Pulmonary<br>•Liver<br>•Renal function |
| | <65 years | 65-75 years |
| | With abnormal:<br>•Cardiac<br>•Pulmonary<br>•Liver<br>•Renal function | With abnormal:<br>•Cardiac<br>•Pulmonary<br>•Liver<br>•Renal function |

Recommendations by A. Palumbo

# Bortezomib dose adjustments

- 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** |

- Once weekly administration enables patients to receive the same overall dose as with the VISTA schedule by increasing the number of treatment cycles

**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**

**Recommendations by A. Palumbo**

# Part 2: Conclusions

- MP + novel agent superior over MP alone
  - MPT: 2/5 studies have demonstrated superior survival over MP
  - VMP: significantly superior survival compared with MP
- VMP allows for treatment-free intervals which may be associated with patient benefits
- Other combinations (VMPT) are feasible and effective
- Dose adjustments should be considered based on age and comorbidities
  - Once-weekly bortezomib schedules result in significant activity with improved tolerability

# The disease has many varieties and there are many treatments : always look at your patient and do what suits him best