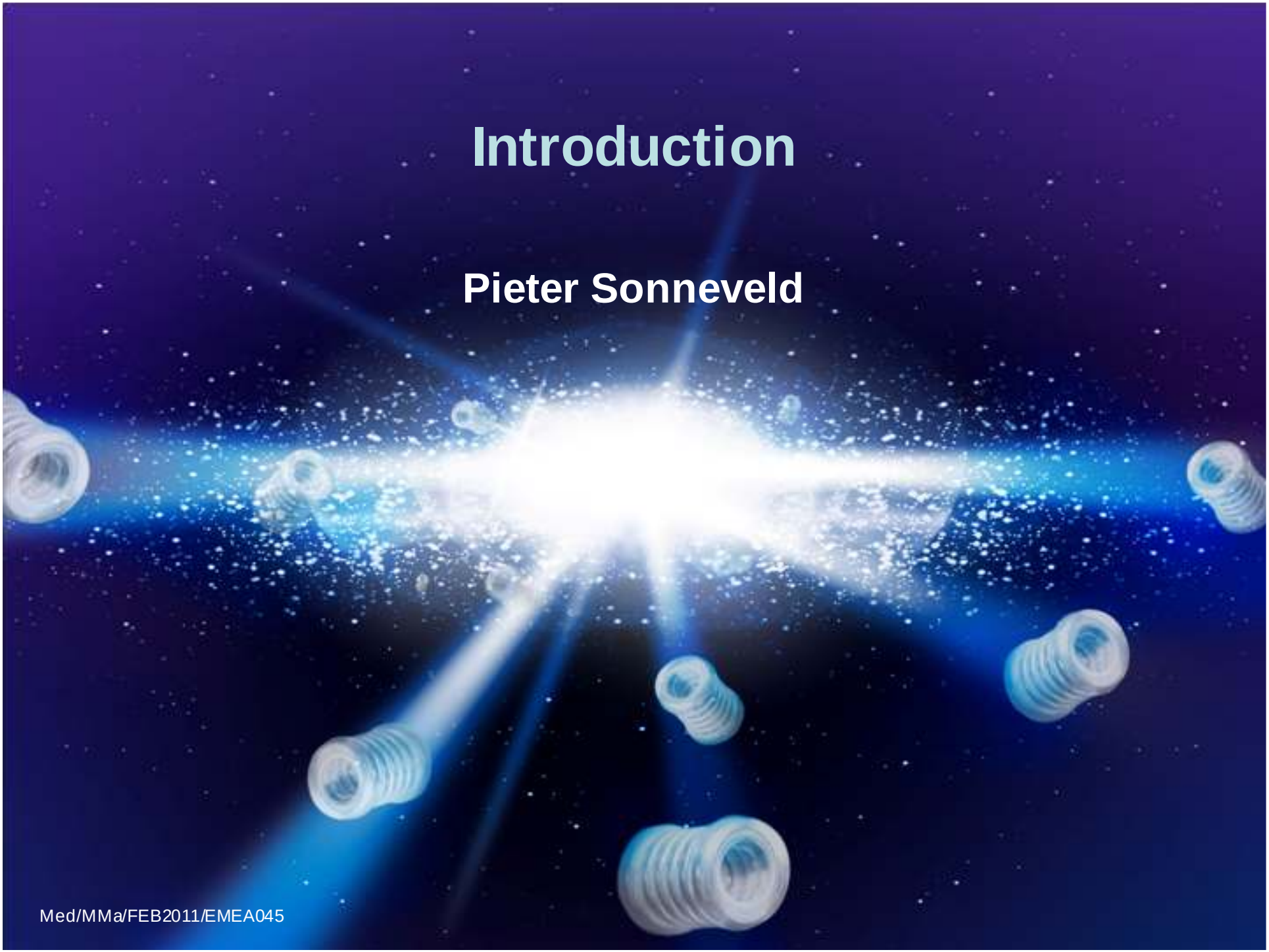

Optimizing Patient Outcomes Through Individualized Treatment Approaches: Phase III Data
Co-Chairs: Robert Orlowski, USA and
Pieter Sonneveld, The Netherlands
Med/MMa/FEB2011/EMEA045


Introduction
Pieter Sonneveld
Med/MMa/FEB2011/EMEA045

Disclosures

Research Support/P.I.	Janssen, Millennium, Celgene
Employee	None
Consultant	Janssen, Millennium, Celgene
Major Stockholder	None
Speakers Bureau	None
Honoraria	Janssen, Millennium, Celgene
Scientific Advisory Board	Janssen, Millennium, Celgene, Onyx

Presentation includes discussion of the off-label use of a drug or drugs

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- The presentations may include discussions on off-label use of drugs

Symposium information

- **Program and Faculty Information book**
  - **Question cards for any questions on the presentations**
  - **Evaluation form – please complete this form**
  - **Slide request form**

Educational objectives

- Discuss treatment goals in multiple myeloma and review the evidence supporting proteasome inhibition as an effective therapy to achieve maximal response
- Review Phase III clinical trial data in the treatment of newly diagnosed multiple myeloma in the transplant and non-transplant settings
- Evaluate management strategies for patients with comorbidities, as well as strategies to improve treatment tolerability
- Discuss practical issues about the management of patients receiving novel agents


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Clinical implications of proteasome inhibition in multiple myeloma: a decade of clinical experience

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Treatment goals and clinical outcomes in multiple myeloma

Robert Orlowski

Med/MMa/FEB2011/EMEA045

Disclosures

Research Support/P.I.	Allos Therapeutics, Bristol-Myers Squibb, Celgene, Johnson & Johnson, Millennium Pharmaceuticals
Employee	None
Consultant	Bristol-Myers Squibb, Celgene, Centocor, Cephalon, Millennium Pharmaceuticals, Novartis
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Scientific Advisory Board	Bristol-Myers Squibb, Celgene, Centocor, Cephalon, Millennium Pharmaceuticals, Novartis

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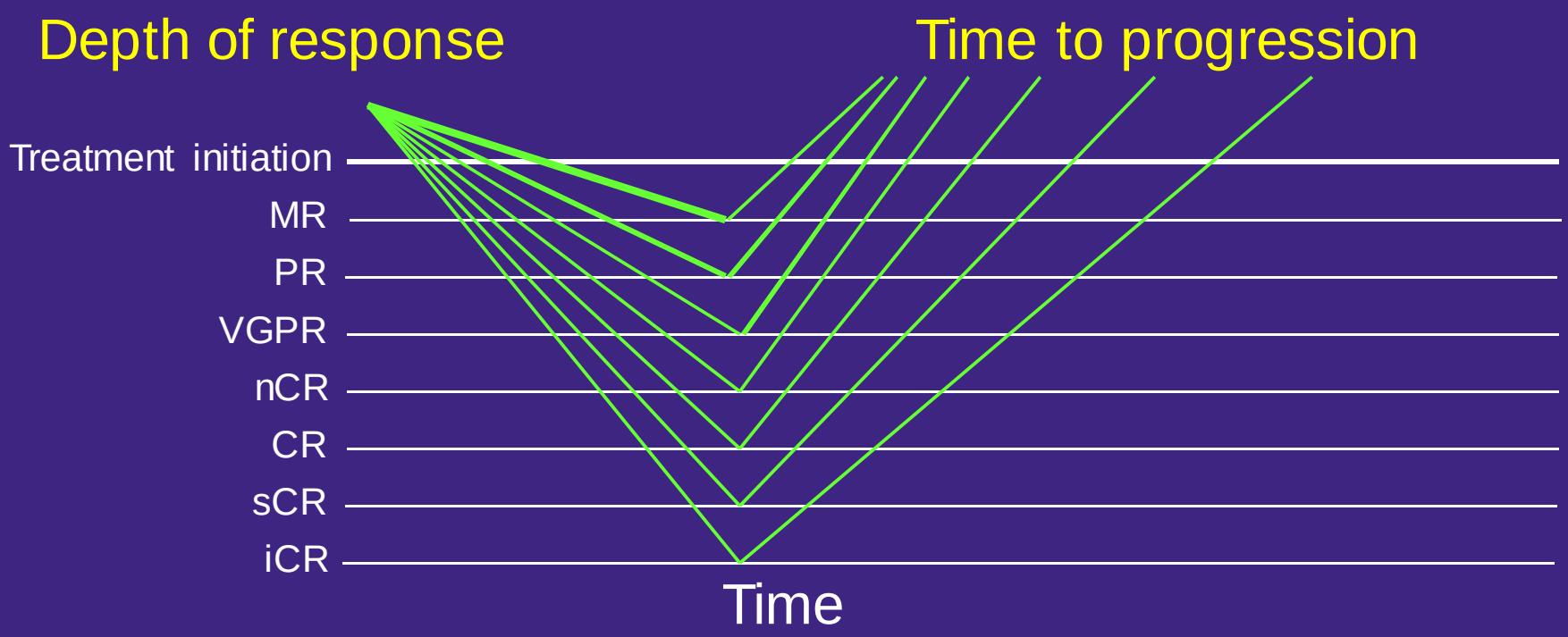
Major treatment goals

- Achieve disease response
- Reduce active symptom burden
- Prevent any additional morbidity
- Prolong the patient’s overall survival
- Ultimately, to cure multiple myeloma altogether

What disease response is best?



- **Depth of response is related to TTP**

Niesvizky et al. Br J Haematol 2008; 143(1): 46-53; Harousseau et al. Blood 2009; 114(15): 3139-3146
Chanan-Khan et al. J Clin Oncol 2010; 28(15): 2612-2624

In transplant patients

- **Meta-analysis of 21 studies**
- **Highly significant association between CR / nCR / VGPR following induction and TTP / EFS / OS (p=0.0001 for time to event, p<0.0027 for OS)**
- **Also between CR / nCR / VGPR following transplant (p<0.00001 for both)**

van de Velde et al. Haematologica 2007; 92(10): 1399-1406

In novel agent era

- **MRC Myeloma IX, CTD vs CVAD**
  - **CR associated with better PFS[1,2]**
- **IFM 2005-01; VD vs VAD**
  - **VGPR or better after induction major PFS factor[3]**
- **GIMEMA; VTD vs VD**
  - **CR/nCR prognostic for PFS[4]**

[1]Morgan et al. Blood 2009; 114(22); Abstract 352 (oral presentation)
[2]Morgan et al. IMW 2009; Abstract A546 (oral presentation)
[3]Moreau et al. Blood 2011; 117(11): 3041-3044
[4]Cavo et al. Lancet 2010; 376(9758): 2075-2085

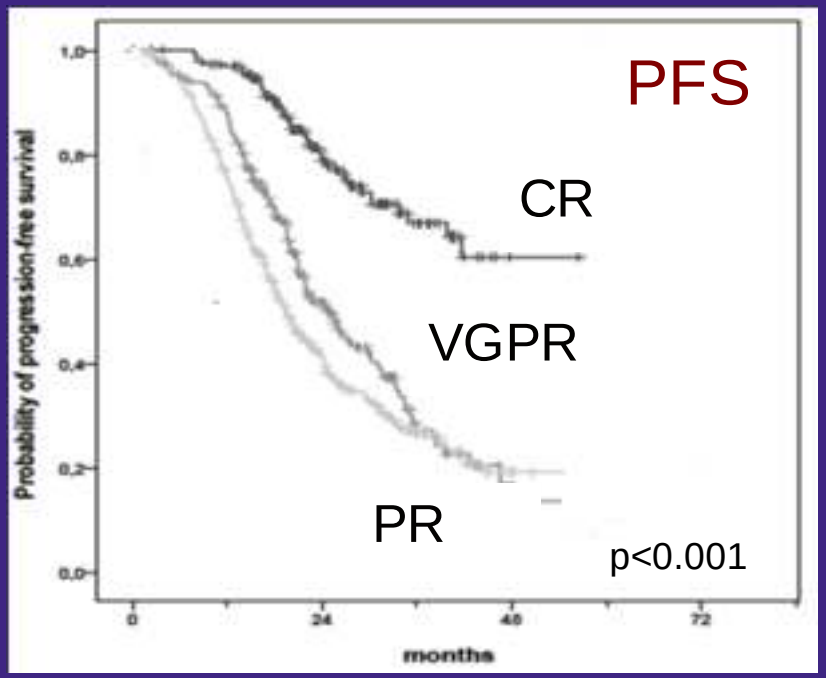
In non-transplant setting

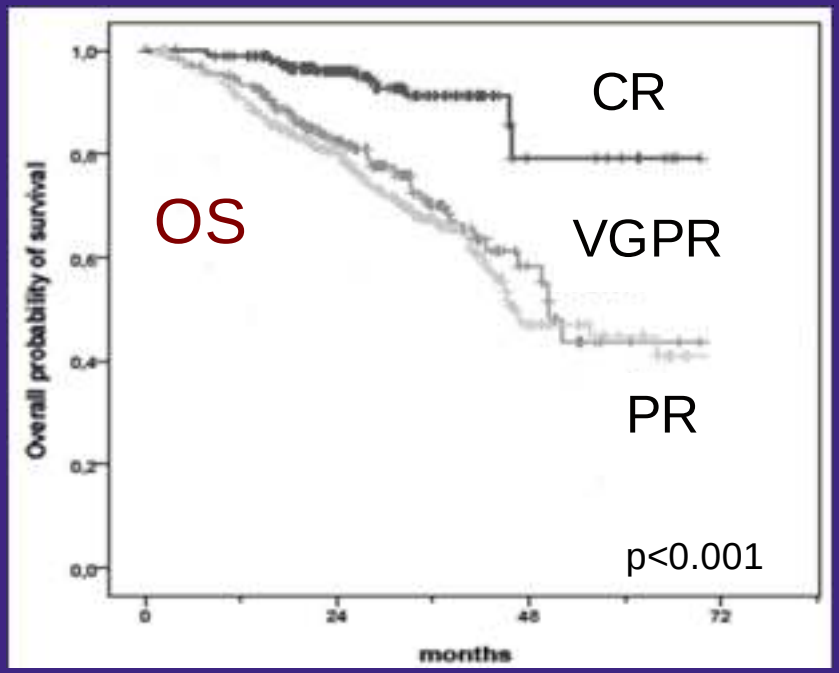
- **GIMEMA trial of MPT vs MP[1]**
  - **Better PFS if in VGPR after 6 months (p=0.02)**
- **MRC Myeloma IX trial of CTDa vs MP[2]**
  - **CR patients had longer PFS/OS (p<0.001)**
- **VISTA trial of VMP vs MP[3]**
  - **Patients in CR had longer TTP (p=0.004), PFS, TTNT**
- **GIMEMA trial of VMPT + VT vs VMP[4]**
  - **Longer PFS for CR vs VGPR and PR**
- **PETHEMA/GEM trial of VMP+VT/VP vs VTP+VT/VP[5]**
  - **Longer PFS if MRD negative status**

[1]Palumbo et al. Blood 2008; 112: 3107-3114
[2]Morgan et al. ASH 2009; Abstract 352 (oral presentation)
[3]Harousseau et al. Blood 2010; 116(19): 3743-3750
[4]Palumbo et al. ASH 2010; Abstract 620 (oral presentation)
[5]Mateos et al. Lancet Oncol 2010; 11: 934-941

CR correlates with survival

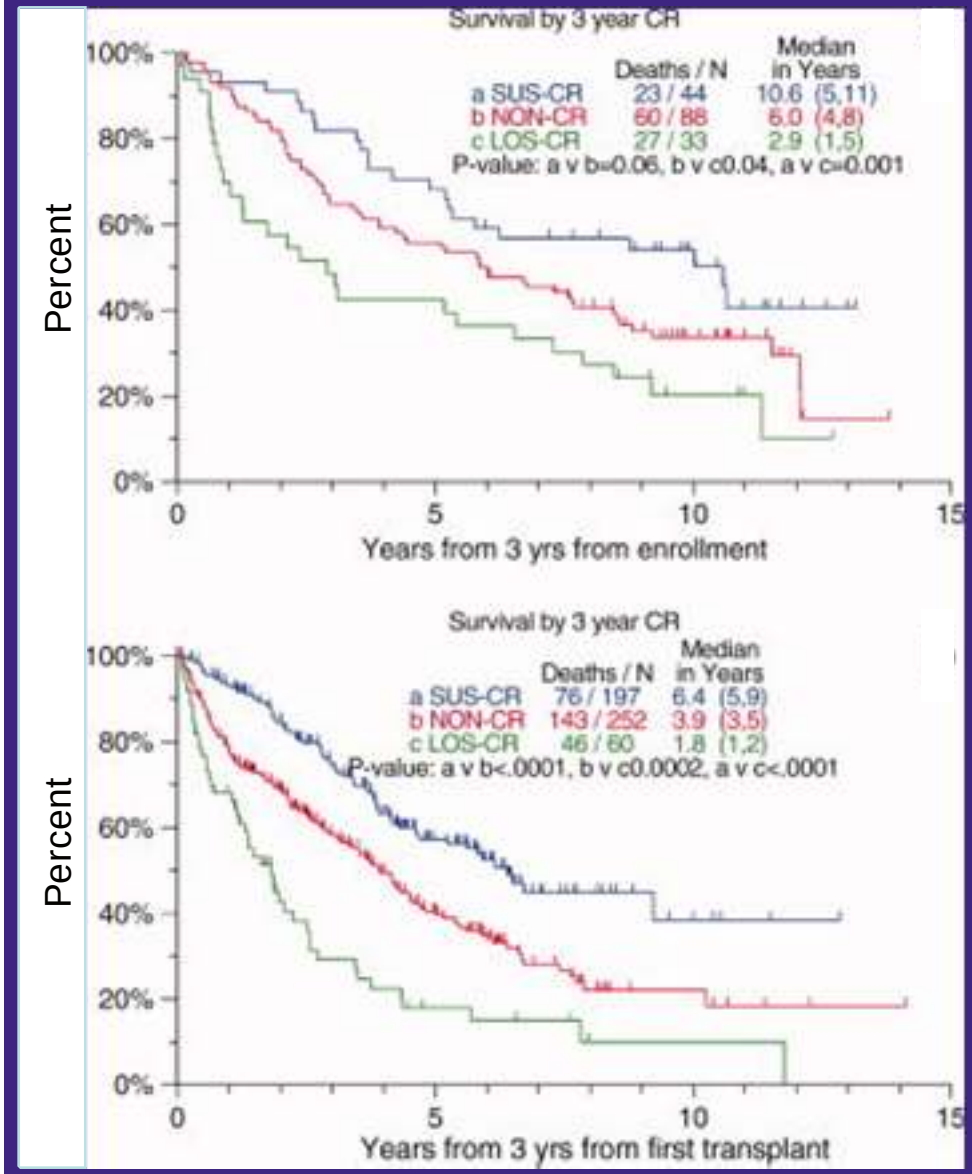
- **Retrospective analysis of three randomized studies from GIMEMA and HOVON (n=1175)**
  - **MP (n=332), MPT (n=332), VMP (n=257), or VMPT-VT (n=254)**





Gay et al. Blood 2011; 117(11): 3025-3031

Achieving and maintaining CR



- Sustaining CR within a 3-year landmark from treatment initiation was associated with a highly superior survival ($p<0.0001$)
  - Achieving and losing CR worse than no CR

Barlogie et al. Cancer 2008; 113(2): 355-359

Value of Immunophenotypic CR

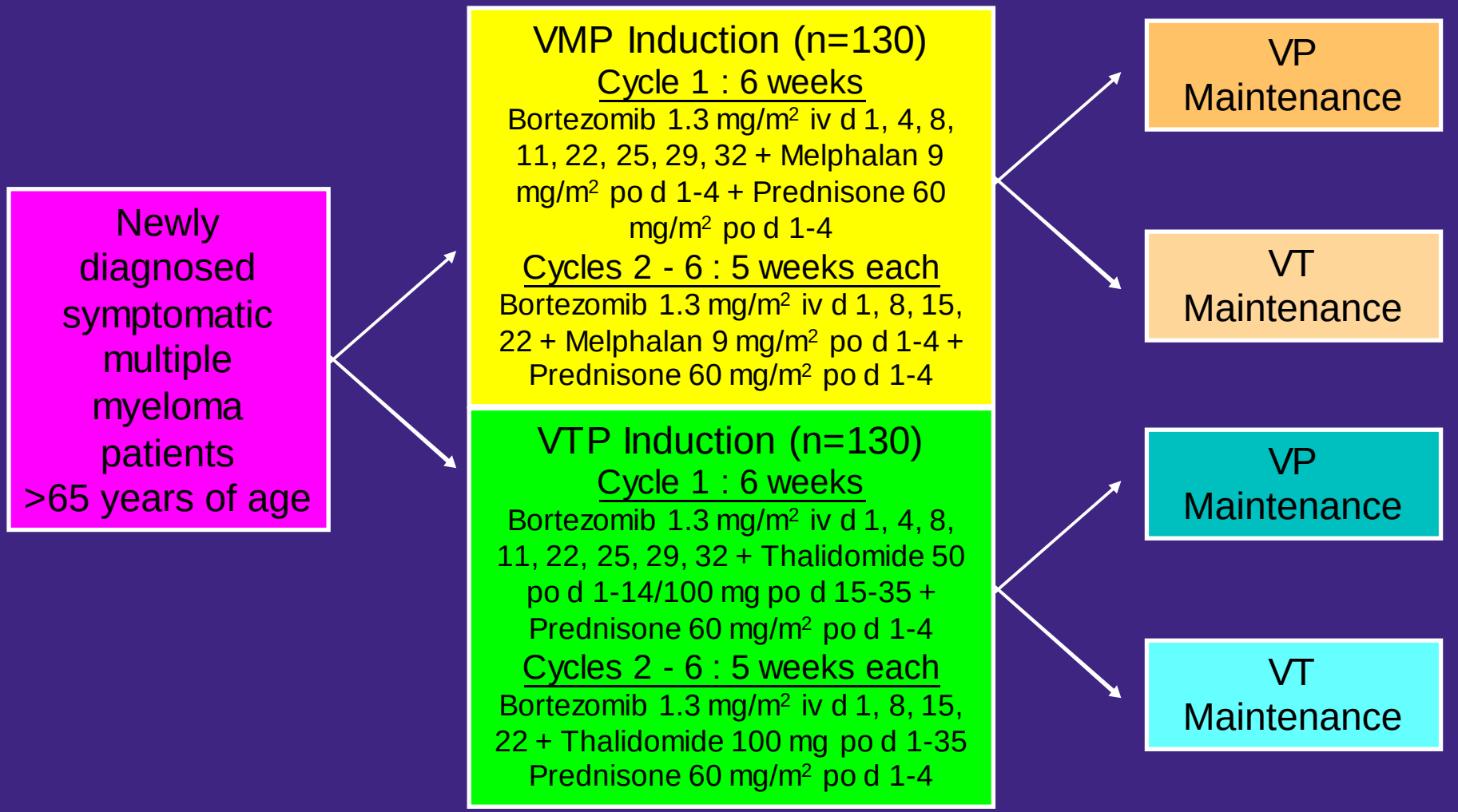
2009 ASH Abstract 3

A Prospective, Multicenter, Randomized, Trial of Bortezomib/Melphalan/Prednisone (VMP) Versus Bortezomib/Thalidomide/Prednisone (VTP) as Induction Therapy Followed by Maintenance Treatment with Bortezomib/Thalidomide (VT) Versus Bortezomib/Prednisone (VP) in Elderly Untreated Patients with Multiple Myeloma Older Than 65 Years

Maria-Victoria Mateos, A. Oriol, J. Martinez, M.T. Cibeira[4], N.C. Gutiérrez[5], M.J. Terol[6], R. de Paz[7], J. García-Laraña[8], E. Bengoechea[9], A.M. García-Sancho[10], R. Martínez[11], L. Palomera[12], F. de Arriba[13], Y. Gonzalez[14], J. Hernández[15], A. Sureda[16], J.-L. Bello[17], J.J. Lahuerta[18], J. Blade[19] and Jesús F. San-Miguel[20]

Mateos et al. Blood 2009; 114(22): Abstract 3 (oral presentation)

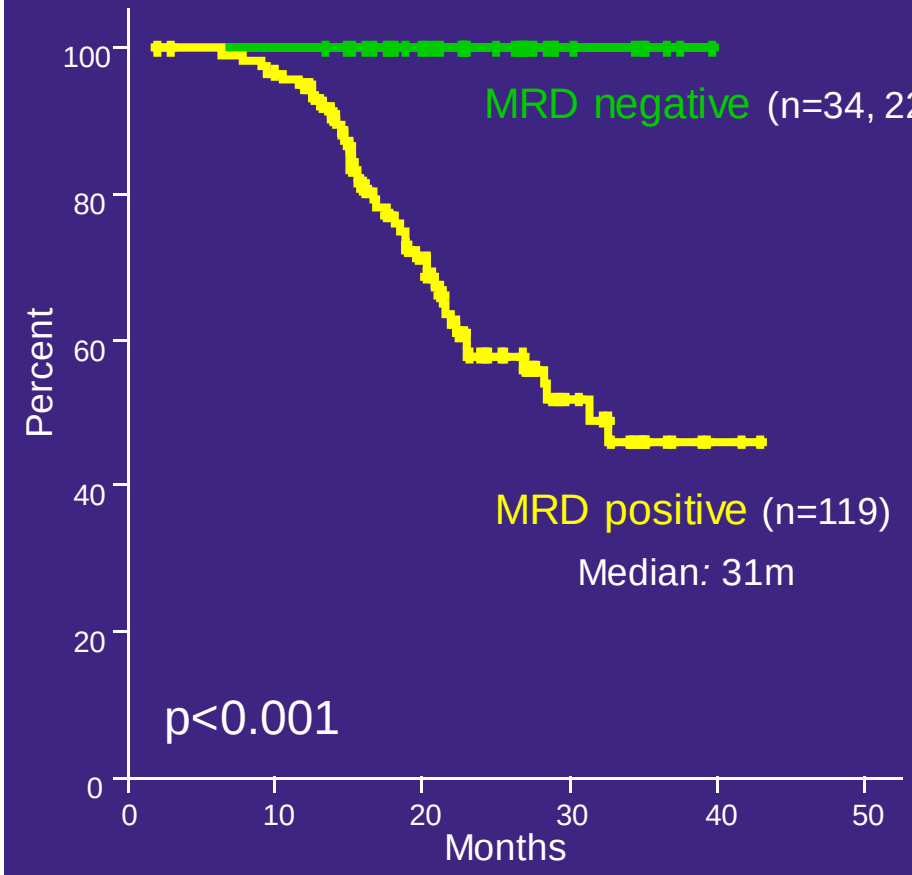
Study design



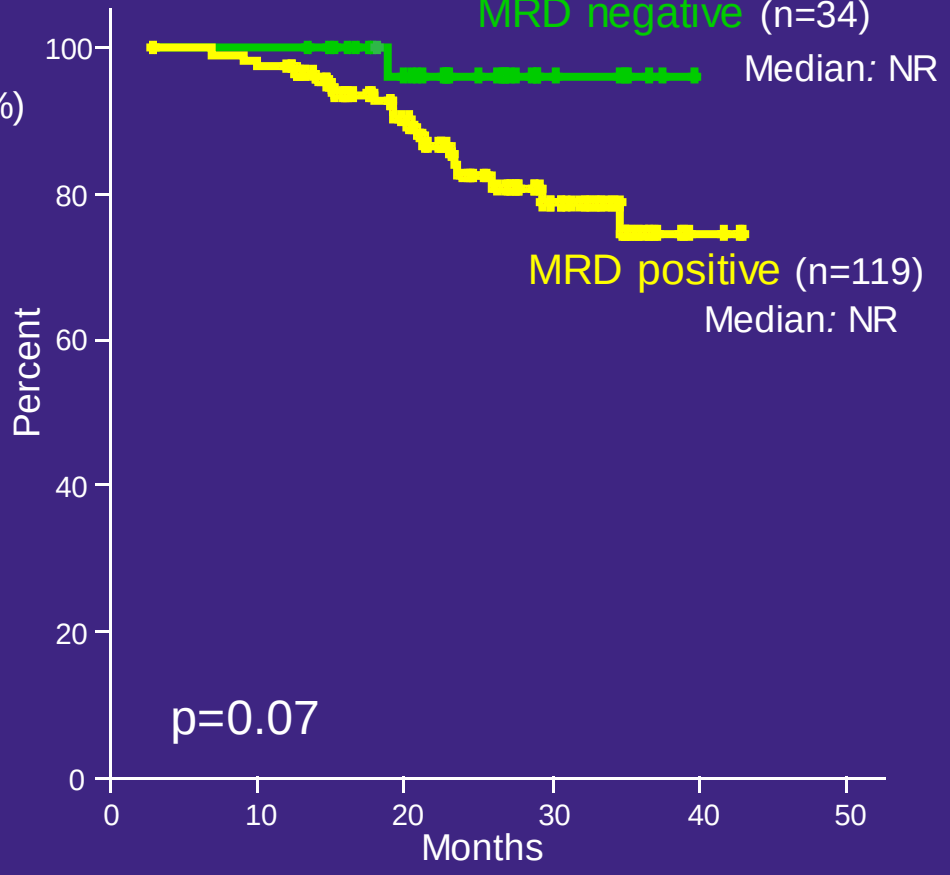
Mateos et al. Blood 2009; 114(22): Abstract 3 (oral presentation)

Immunophenotypic CR & outcome

TTP



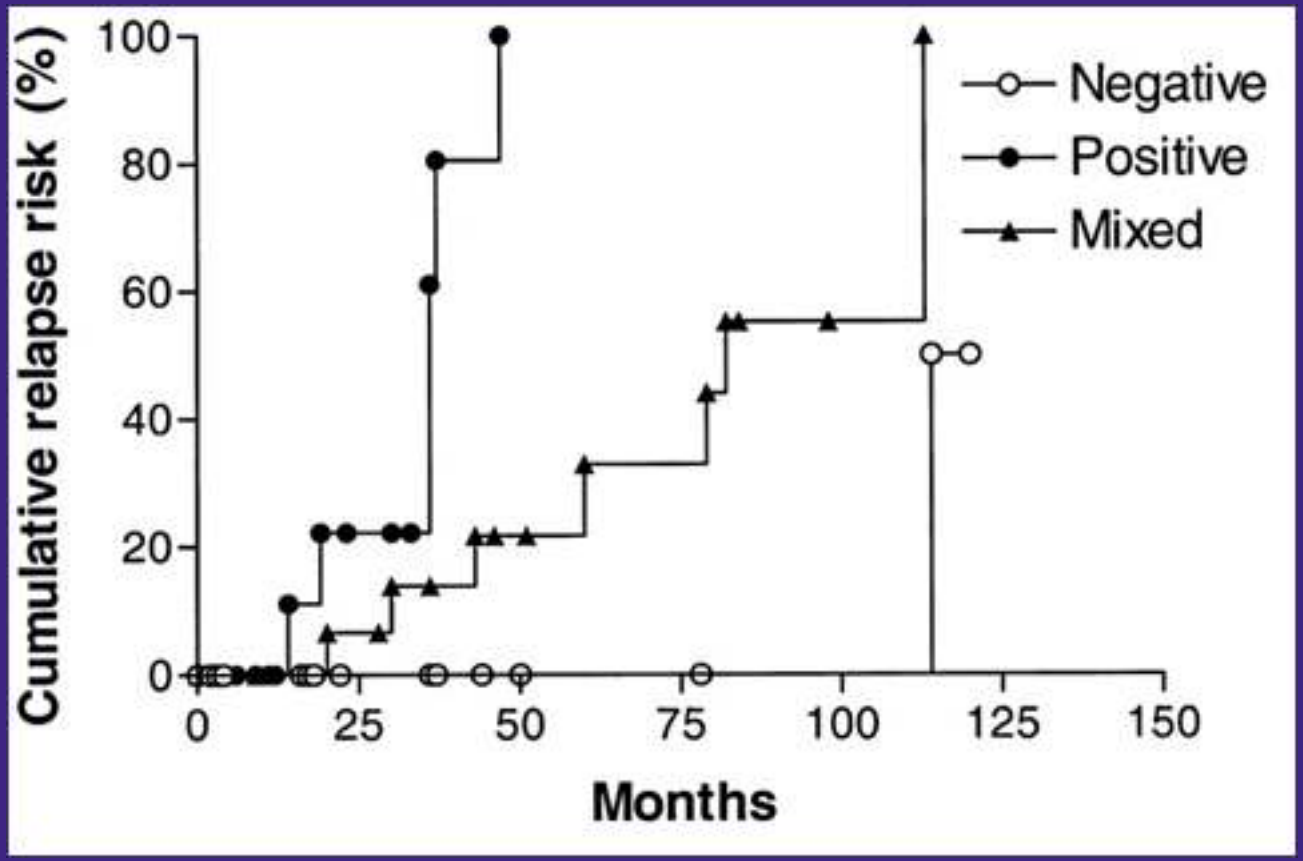
OS



Mateos et al. Blood 2009; 114(22): Abstract 3 (oral presentation)

Molecularly defined CR?

- **PCR-based Ig re-arrangement assay in patients s/p allo-SCT**



Corradini et al. Blood 2003; 102(5): 1927-1929

Other treatment goals

- **Target rational pathway**
  - **Multiple key downstream targets to pathobiology**
- **Maximize the quality of life**
  - **Enhance TTNT, TFI**
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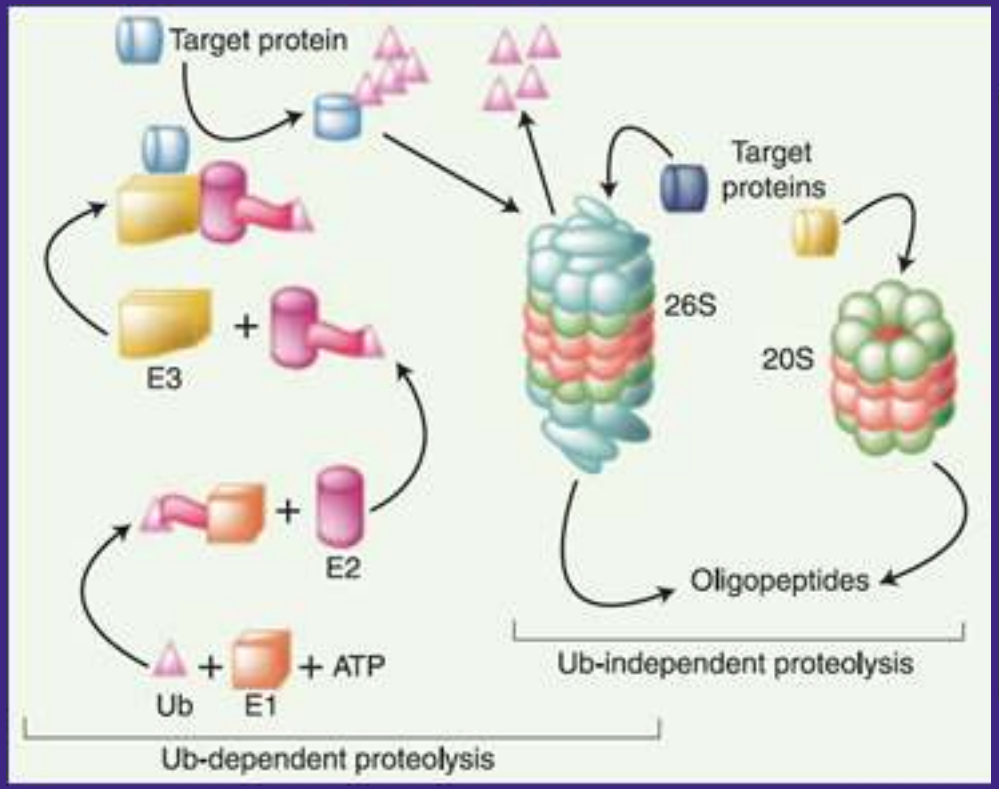
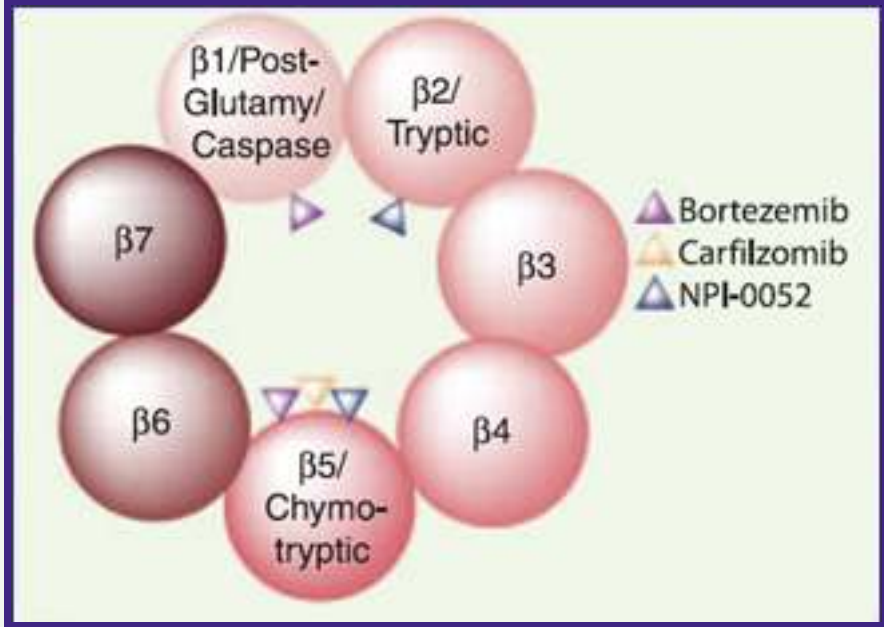
  - **Don’t break the bank while breaking multiple myeloma**

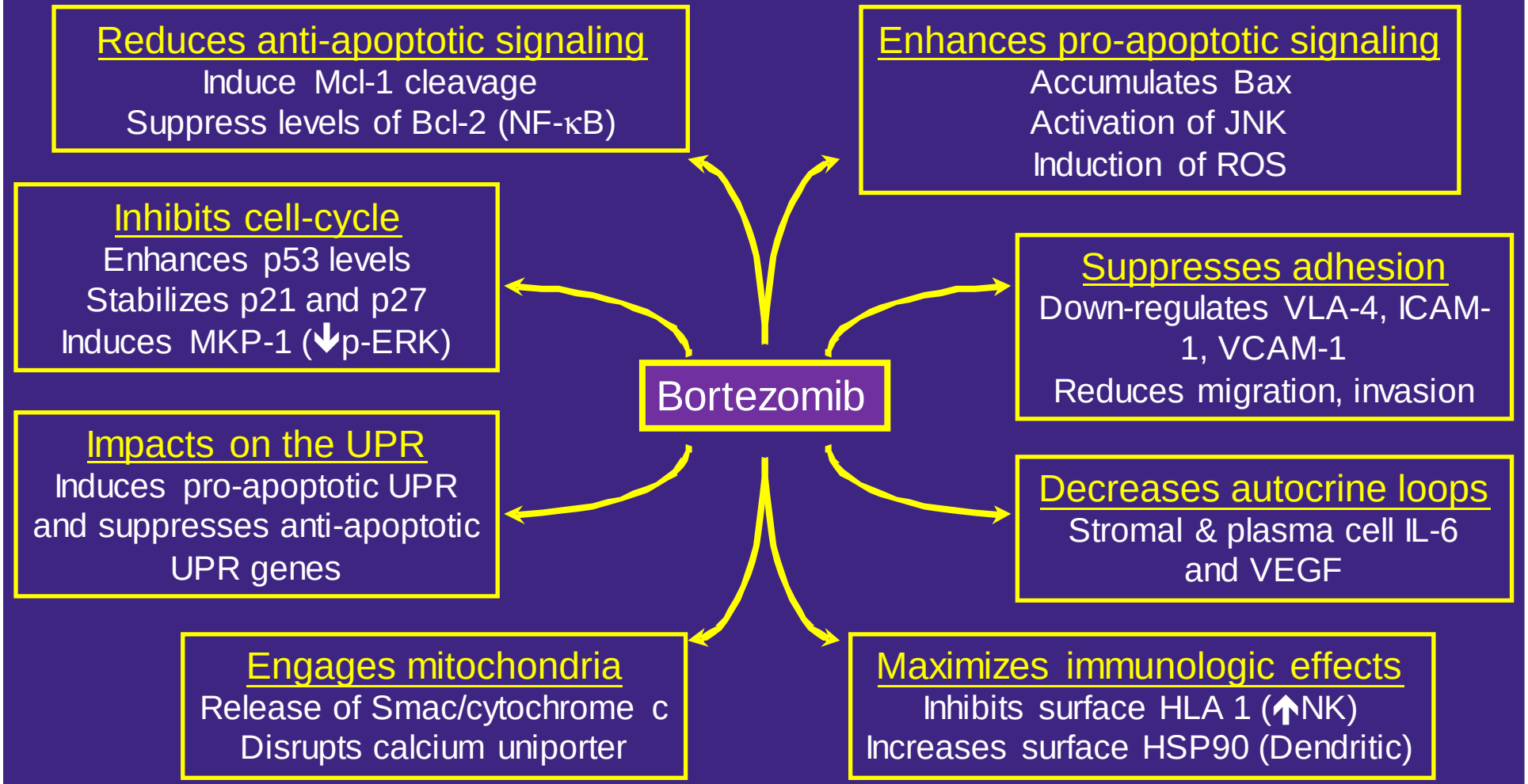
Bortezomib and the proteasome





Orlowski et al. Clin Cancer Res 2008; 14(6): 1649-1657

Mechanisms: Effects in myeloma



Shah & Orlowski. Leukemia 2009; 23(11): 1964-1979

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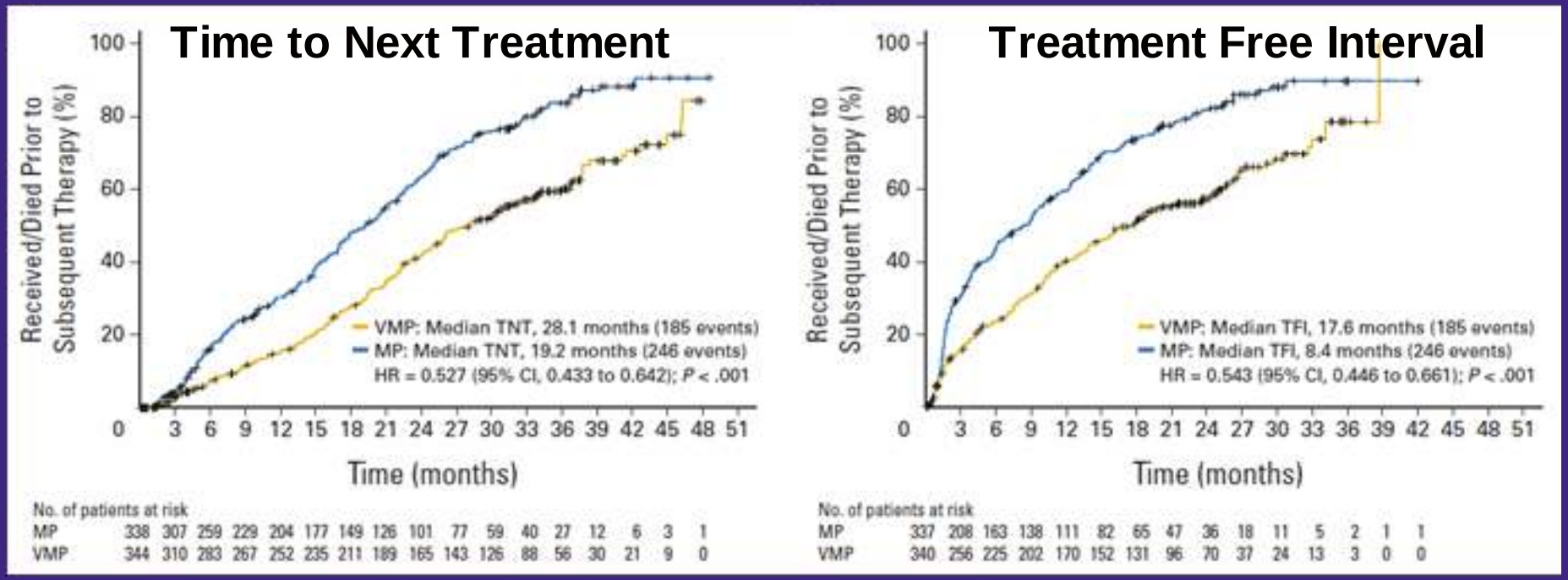
TTNT and TFI



- **Superior induction maximizes TTNT and TFI**

Mateos et al. J Clin Oncol 2010;28: 2259-2266

Also true in relapsed setting

	CR (n=27)	VGPR (n=31)	PR (n=77)	Total (n=315)
Median TFI, months	24.1	6.9	6.4	4.8
Median TTAT, months	27.1	13.6	14.0	10.6

- TFI longer for CR vs VGPR (p=0.007) and PR (p=0.002)
- TTAT better for CR vs VGPR (p=0.007) and vs PR (p=0.002)

TTAT, time to alternative treatment

Niesvizky et al. Br J Haematol 2008; 143(1): 46-53

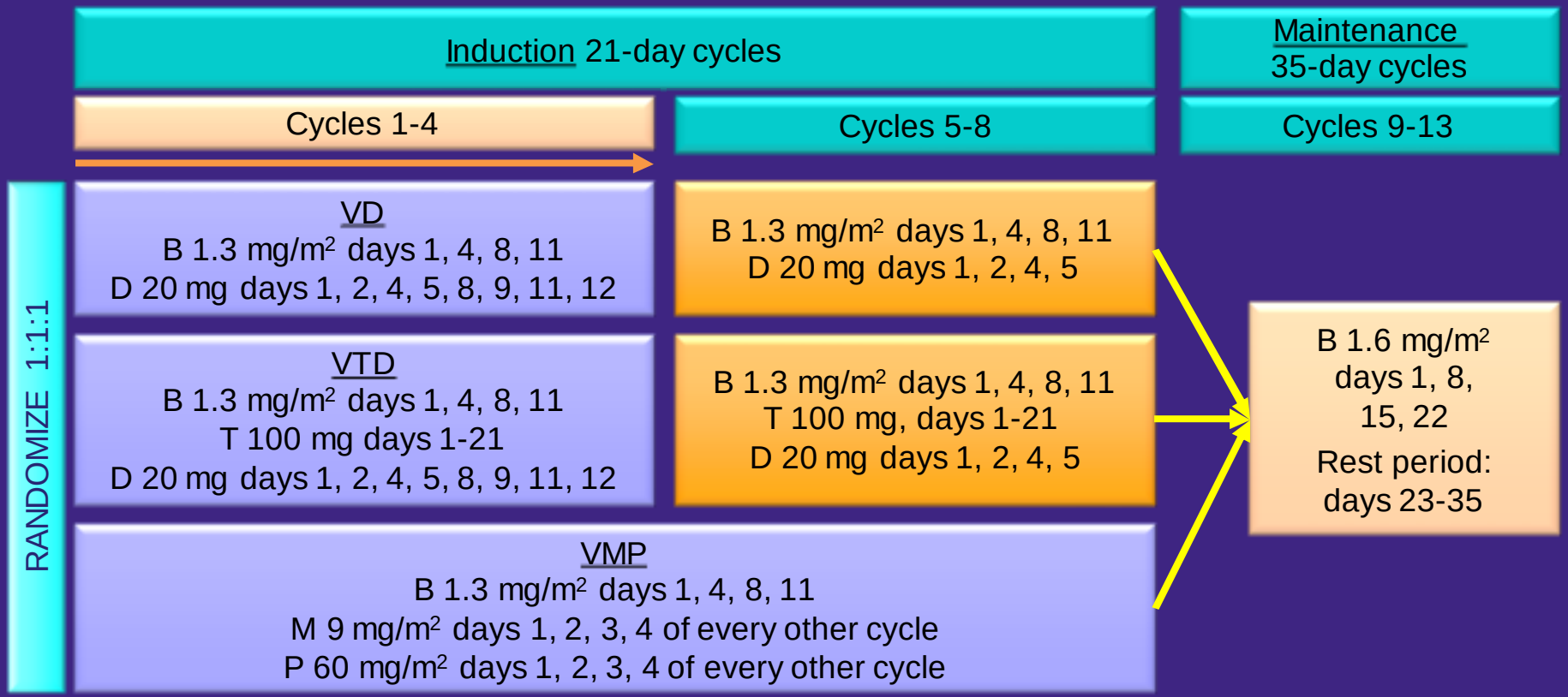
2010 ASH Abstract 619

Phase 3b UPFRONT Study : Safety and Efficacy of Weekly Bortezomib Maintenance Therapy After Bortezomib-Based Induction Regimens In Elderly, Newly Diagnosed Multiple Myeloma Patients

Ruben Niesvizky, Ian W. Flinn, Robert M. Rifkin, Nashat Y Gabrail, Veena Charu, Billy Clowney, James Essell, Yousuf A Gaffar, Thomas A. Warr, Rachel Neuwirth, Deyanira Corzo, and James A Reeves

Niesvizky et al. Blood 2010; 116(21): Abstract 619 (oral presentation)

Study design

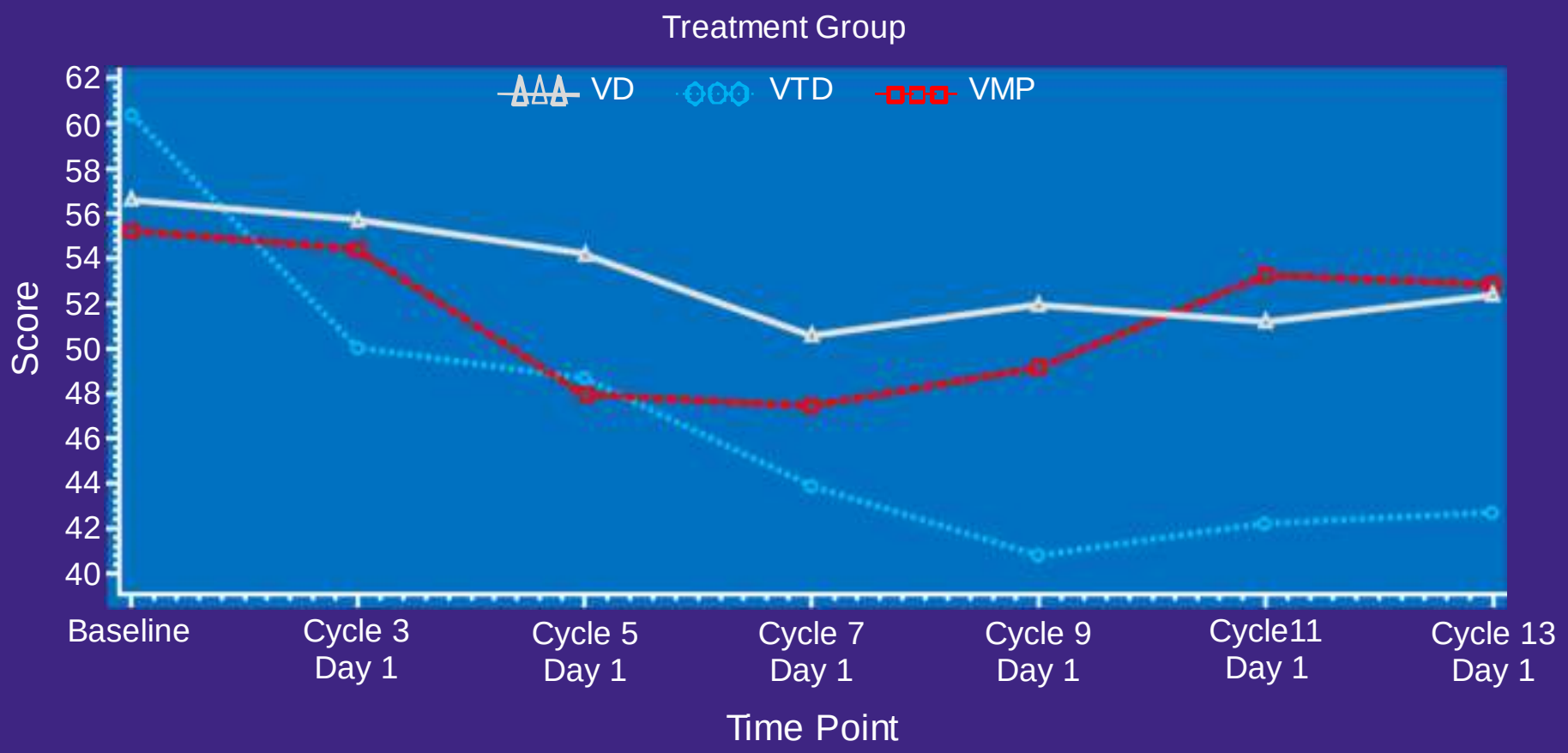


BD and BTD: reduced dexamethasone dosing in cycles 5-8 vs 1-4

- **Endpoints: primary – PFS; secondary – ORR, safety, QoL**
- **Patients: results reported after 100 patients in each arm had the opportunity to complete all 13 treatment cycles (8 induction cycles and 5 maintenance cycles)**

Niesvizky et al. Blood 2010; 116(21): Abstract 619 (oral presentation)

Patient-reported quality of life



Niesvizky et al. Blood 2010; 116(21): Abstract 619 (oral presentation)

Other treatment goals

- **Target rational pathway**
  - **Multiple key downstream targets to pathobiology**
- **Maximize the quality of life**
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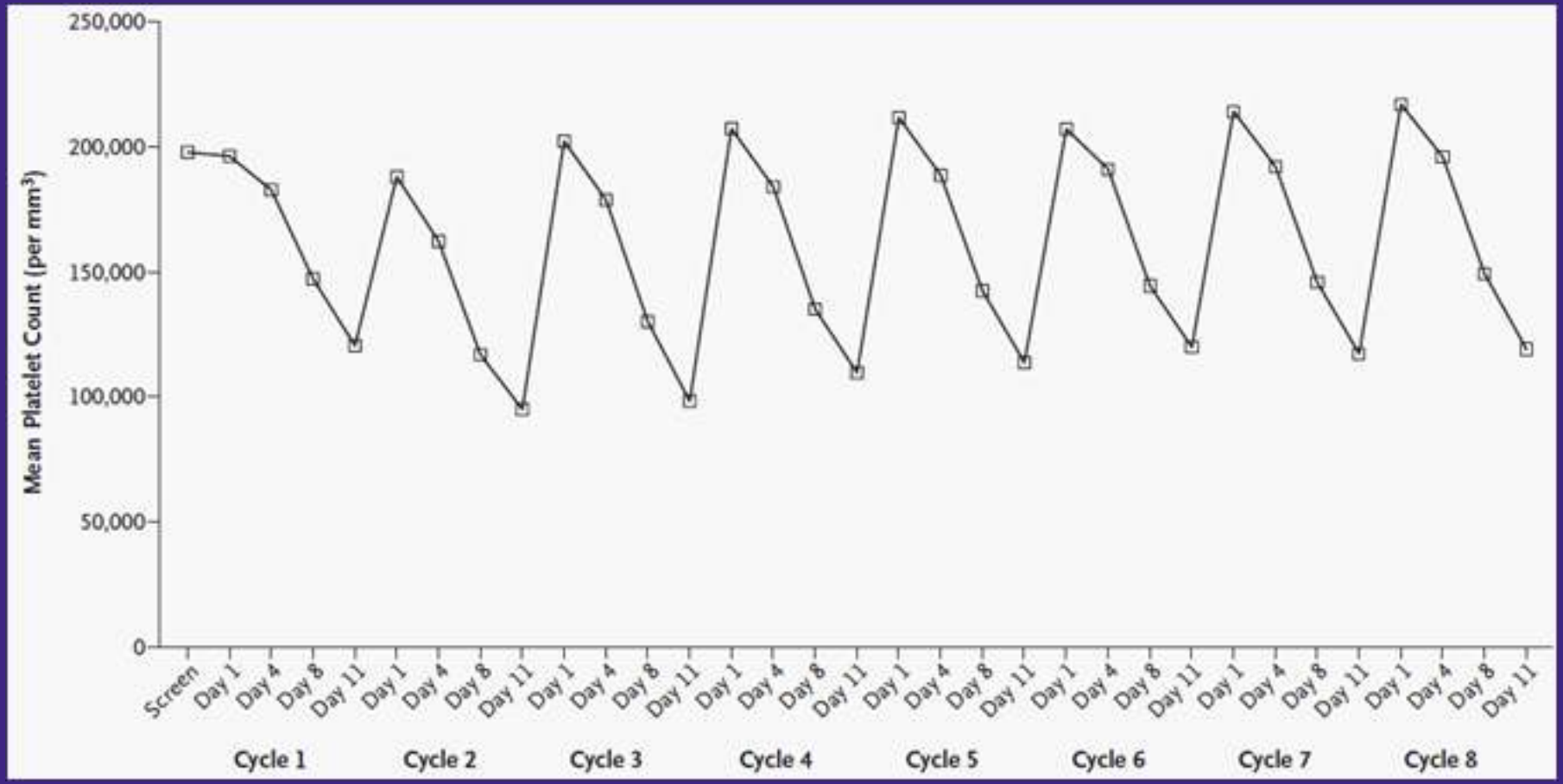
Bortezomib & thrombocytopenia



Richardson et al. New Engl J Med 2005; 352(24): 2487-2498

2010 ASH Abstract 312

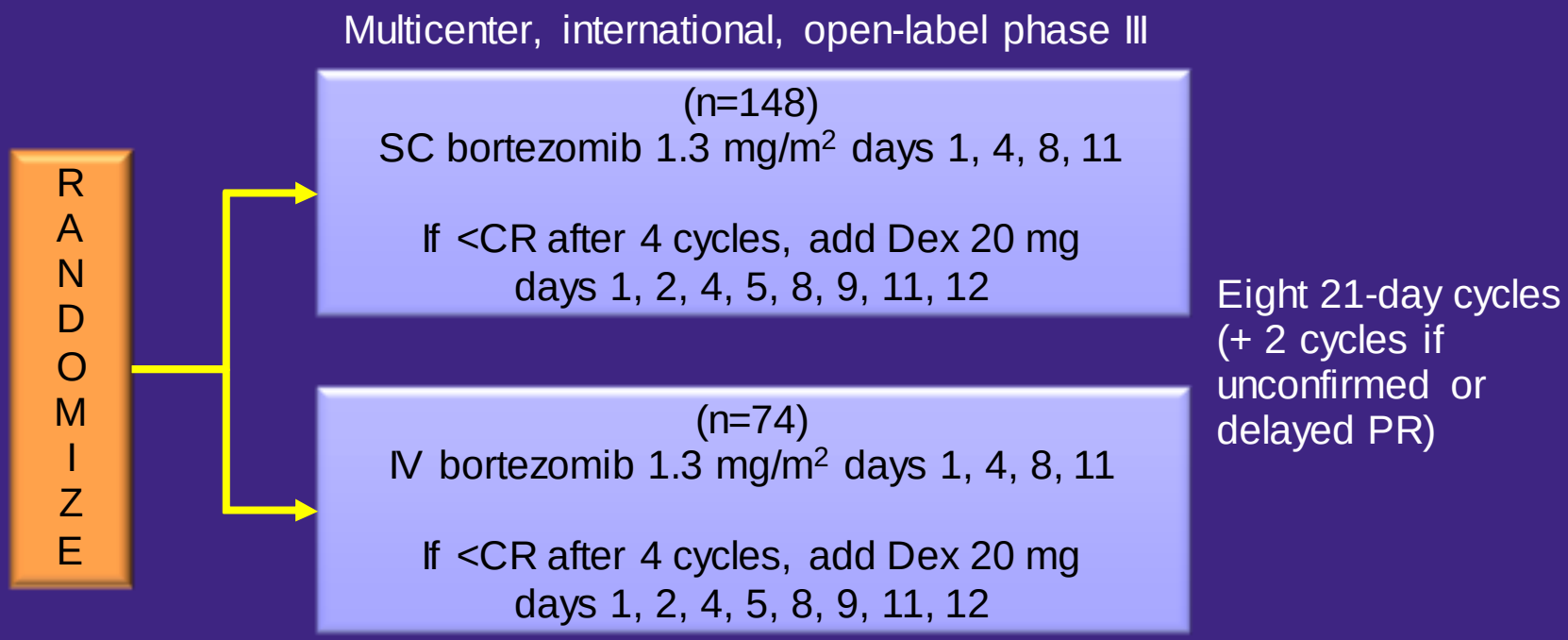
A Phase 3 Prospective Randomized International Study (MMY-3021) Comparing Subcutaneous and Intravenous Administration of Bortezomib In Patients with Relapsed Multiple Myeloma

Philippe Moreau[1*], Halyna V Pylypenko[2*], Sebastian Grosicki[3*], Evgeniy E Karamanesht[4*], Xavier Leleu[5], Maria E Grishunina[6*], Grigoriy B Rekhtman[7*], Zvenyslava Masliak[8*], Tadeusz Robak[9], Anna V Shubina[10*], Jean-Paul Fermand[11*], Martin Kropff[12], James Cavet[13*], Sudha Parasuraman[14], Huaibao Feng[15*], Donna M Skee[15*], Helgi van de Velde[16*], William M Deraedt[16*] and Jean-Luc Harousseau[17]

Moreau et al. Blood 2010; 116(21): Abstract 312 (oral presentation)

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

Study design



- **Non-inferiority design with at least 60% retention of IV treatment effect by primary endpoint**
- **Endpoints: primary – ORR after 4 cycles; secondary – CR, nCR, VGPR after 4 cycles, ORR after 8 cycles (including effect of Dex), DOR, TTP, PFS, 1-year survival, TTR; other – safety, tolerability, PK, PD**
- **Eligibility criteria: relapsed disease, no prior bortezomib, 1-3 prior lines of therapy, no grade ≥2 PN or neuropathic pain**

Moreau et al. Blood 2010; 116(21): Abstract 312 (oral presentation)

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

Peripheral neuropathy

	Bortezomib IV (N=74)	Bortezomib SC (N=148)	p-value
Any PN event, %	53	38	0.04
Grade ≥2, %	41	24	0.01
Grade ≥3, %	16	6	0.03
Risk factors for PN, %			
Grade 1 PN at baseline	28	23	
Diabetes at baseline	11	13	
Exposure to prior neurotoxic agents	85	86	

Moreau et al. Blood 2010; 116(21): Abstract 312 (oral presentation)

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

SNPs and bortezomib neuropathy

Grade 2-4 peripheral neuropathy (n=15) versus no peripheral neuropathy (n=134) after one cycle of bortezomib				
225189_s_at	*RAPH1*	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	2·24	$3·04\times10^{-2}$
235014_at	*LOC147727*	Hypothetical protein LOC147727	2·15	$1·91\times10^{-2}$
1569872_a_at	*LOC650392*	Hypothetical protein LOC650392	1·98	$9·65\times10^{-4}$
213056_at	*FRMD4B*	FERM domain containing 4B	1·74	$8·42\times10^{-3}$
227984_at	*LOC650392*	Hypothetical protein LOC650392	1·71	$1·19\times10^{-3}$
225478_at	*MFHAS1*	Malignant fibrous histiocytoma amplified sequence 1	1·68	$5·34\times10^{-4}$
226913_s_at	*SOX8*	SRY (sex determining region Y)-box 8	1·68	$4·28\times10^{-13}$
204810_s_at	*CKM*	Creatine kinase, muscle	1·67	$1·11\times10^{-16}$
1569871_at	*LOC650392*	Hypothetical protein LOC650392	1·65	$1·77\times10^{-19}$
228057_at	*DDIT4L*	DNA-damage-inducible transcript 4-like	1·59	$5·59\times10^{-20}$
Grade 2-4 peripheral neuropathy (n=44) versus no peripheral neuropathy (n=78) after two or three cycles of bortezomib				
205590_at	*RASGRP1*	RAS guanyl releasing protein 1 (calcium and DAG regulated)	2·97	$2·14\times10^{-2}$
204527_at	*MYO5A*	Myosin VA (heavy chain 12, myoxin)	1·93	$3·21\times10^{-2}$
235065_at	..	..	1·57	$3·19\times10^{-3}$
205422_s_at	*ITGBL1*	Integrin, β-like 1 (with EGF-like repeat domains)	1·44	$1·35\times10^{-3}$
228113_at	*RAB37*	RAB37, member of RAS oncogene family	1·41	$3·69\times10^{-2}$
210321_at	*GZMH*	Granzyme H (cathepsin G-like 2, protein h-CCPX)	1·37	$3·19\times10^{-2}$
226969_at	*MTR*	5-methyltetrahydrofolate-homocysteine methyltransferase	1·34	$4·26\times10^{-2}$
204072_s_at	*FRY*	Furry homolog (*Drosophila*)	1·31	$4·94\times10^{-2}$
236442_at	*DPF3*	D4, zinc and double PHD fingers, family 3	1·30	$3·38\times10^{-2}$
243329_at	..	..	1·30	$4·26\times10^{-2}$

- **Different genes in early and late bortezomib-induced PN**

Broyl et al. Lancet Oncol 2010; 11(11): 1057-1065

Other treatment goals

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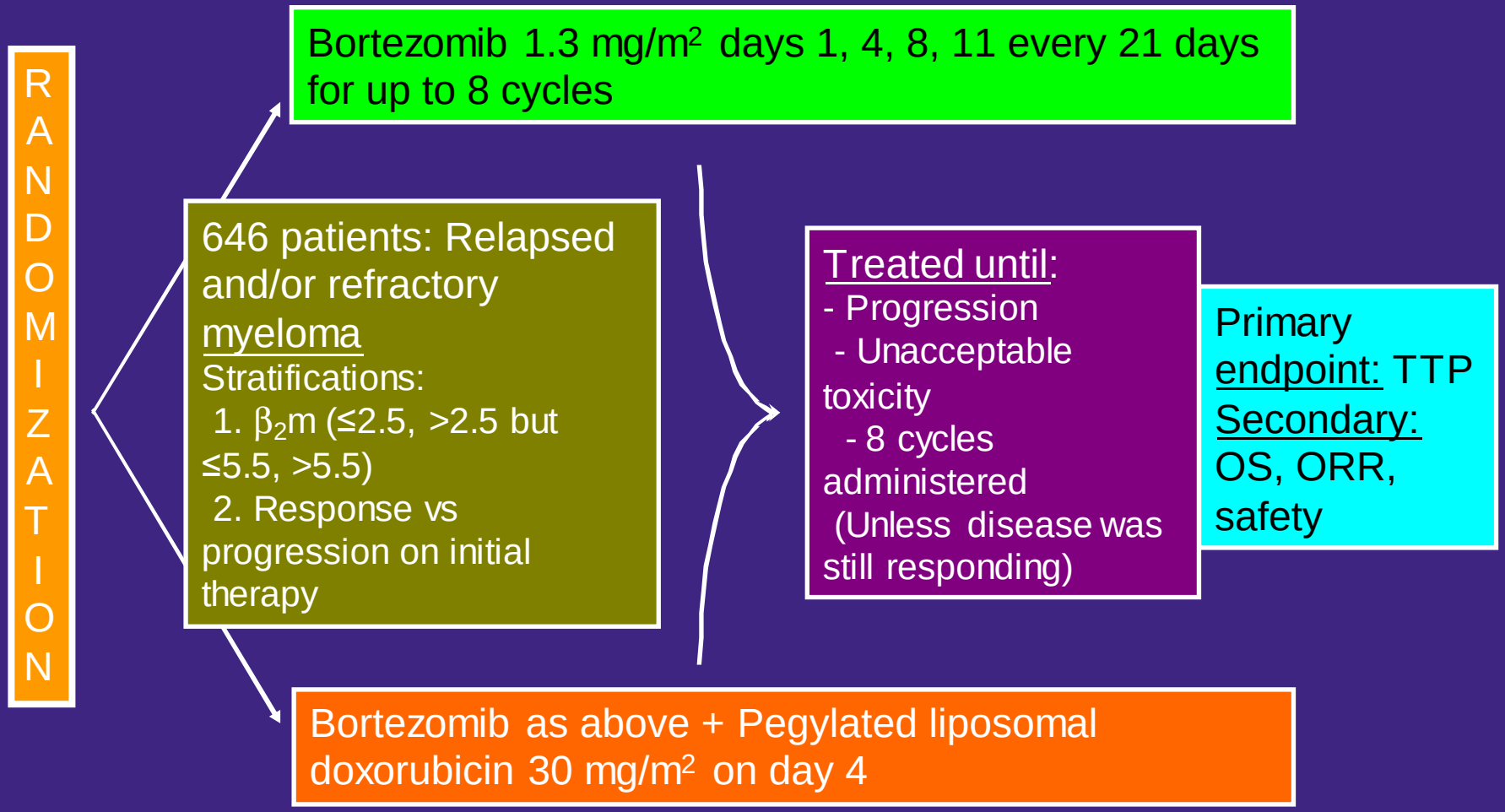
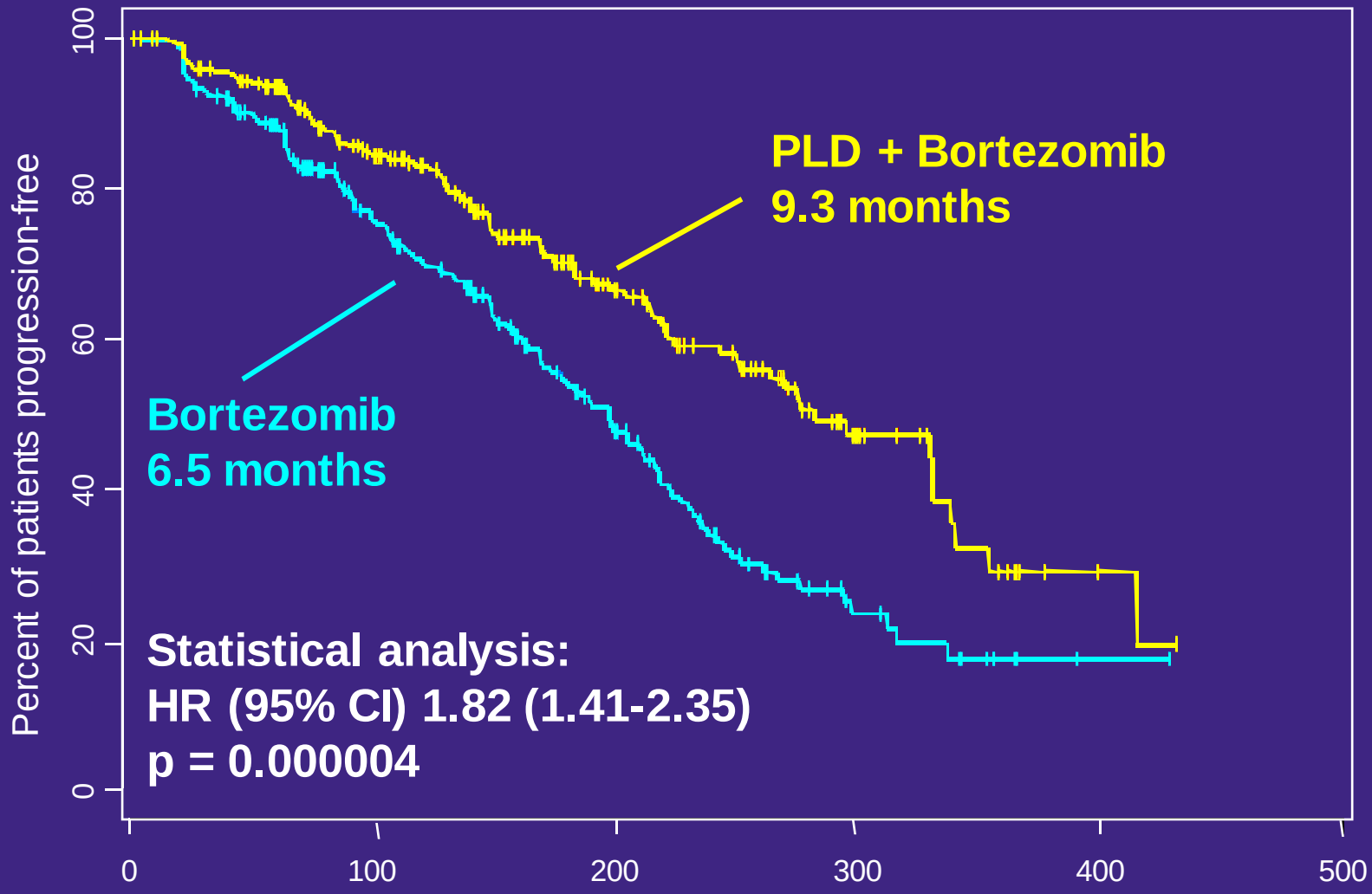


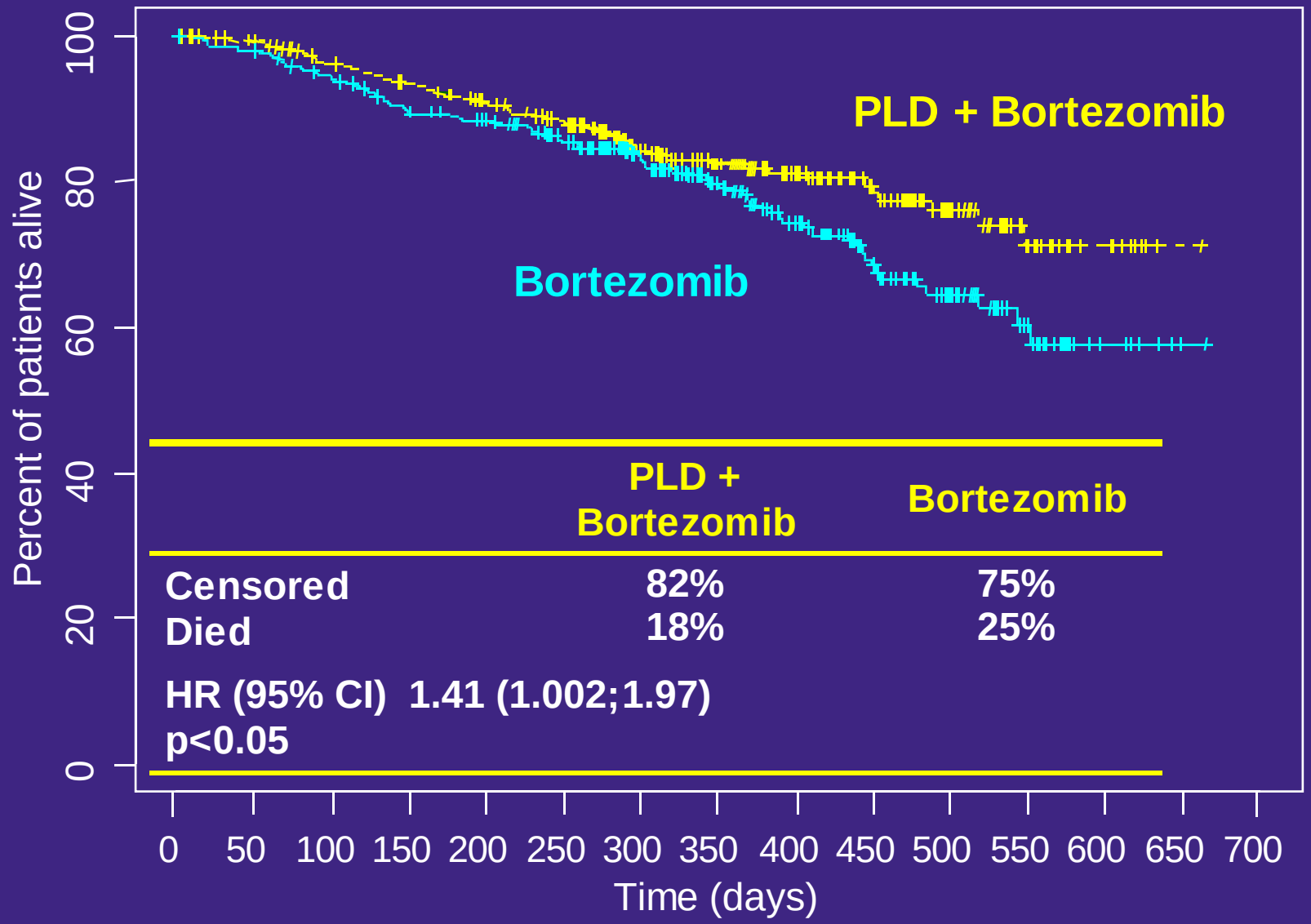
Orlowski et al. J Clin Oncol 2007;25(25):3892-3901

Time to progression



Orlowski et al. J Clin Oncol 2007;25(25):3892-3901

Updated overall survival



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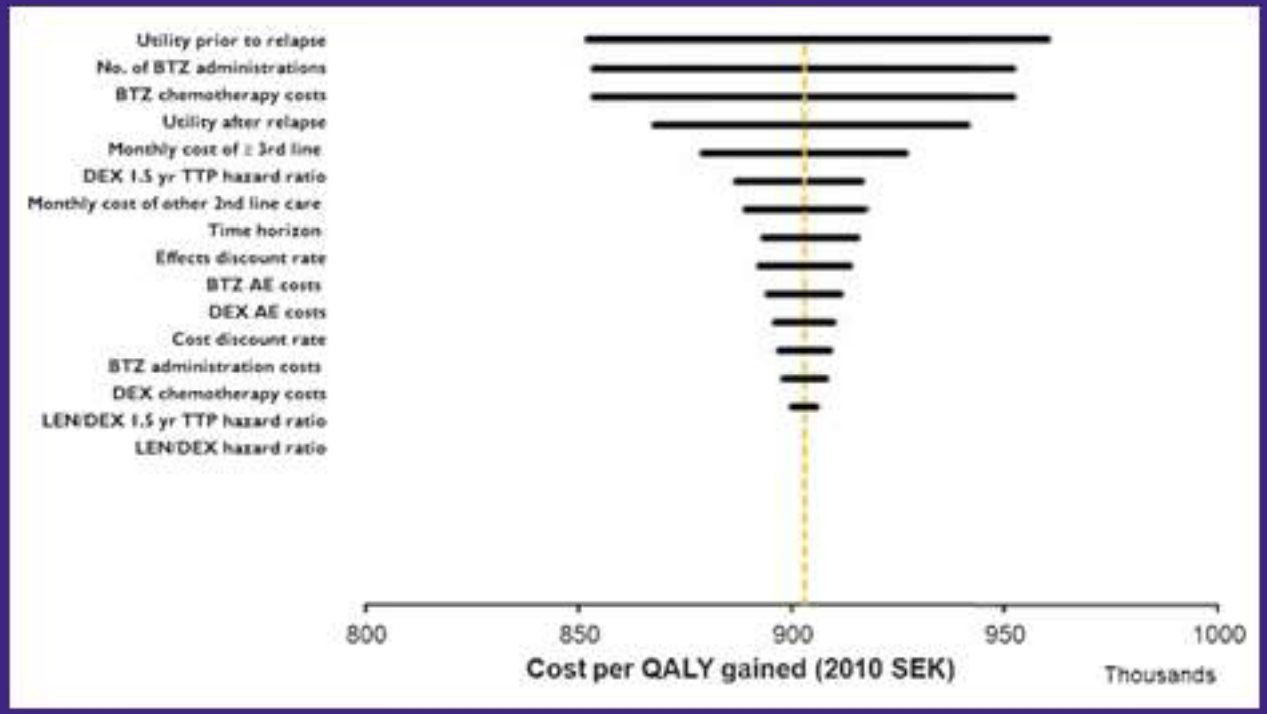
Cost per quality-adjusted life years

- **Swedish perspective: Bortezomib was cost-effective compared to Dex, and Len/Dex**



In relapsed and relapsed/refractory setting

Hornberger et al. Eur J Haematol 2010; 85(6): 484-491

Other comparisons

- **Cost-effective treatment option for advanced multiple myeloma in comparison to best supportive care or thalidomide[1]**
- **In the front line setting, cost effectiveness found to be "within commonly accepted pharmacoeconomic thresholds"[2]**

[1]Mehta et al. Manag Care Interface 2004;17(9): 52-61
[2]Messori et al. Pharmacoeconomics 2011;29(4): 269-285

Conclusions

- **Bortezomib highly effective across disease stages and patient subgroups[1-9]**
  - **Overcomes many high-risk features**
- **Extensive experience to draw upon regarding dosing and side effect management[6,7,10]**
- **Crucial part of our armamentarium as we strive to achieve the best quality disease responses**
  - **Anabolic bone effect provide additional benefits[11]**

[1]*Harousseau et al. J Clin Oncol 2010; 28(30): 4621-4629*
[2]*Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)*
[3]*Cavo et al. Lancet 2010; 376(9758): 2075-2085*
[4]*San Miguel et al. N Engl J Med 2008; 359(9): 906-917*
[5]*Mateos et al. J Clin Oncol 2010; 28: 2259-2266*
[6]*Palumbo et al. J Clin Oncol 2010; 28: 5101-5109*
[7]*Mateos et al. Lancet Oncol 2010; 11: 934-941*
[8]*Richardson et al. Blood 2007; 110: 3557-3560*
[9]*Dimopoulos et al. J Clin Oncol 2010; 28(33): 4976-4984*
[10]*Moreau et al. Lancet Oncol 2011 [Epub ahead of print]*
[11]*Delforge et al. Eur J Haematol 2011 Mar 2 [Epub]*


Optimizing Patient Outcomes Through Individualized Treatment Approaches: Phase III Data
Co-Chairs: Robert Orlowski, USA and
Pieter Sonneveld, The Netherlands
Med/MMa/FEB2011/EMEA045


Improving outcomes for patients not eligible for transplantation
Paul G Richardson
Med/MMa/FEB2011/EMEA045

Disclosures

Research Support/P.I.	Millennium, Celgene
Employee	None
Consultant	None
Major Stockholder	None
Speakers Bureau	None
Honoraria	None
Scientific Advisory Boards	Millennium, Celgene, J&J

Presentation includes discussion of the off-label use of a drug or drugs

Considerations for the treatment of elderly pts

- Relative survival in MM decreases with increasing age[1,2]
  - Advanced age associated with poor outcome using conventional treatments
- Heterogeneous population[1,2]
  - Fit versus frail
  - Comorbidities, e.g. renal function declines with age, cardiac disease, pulmonary dysfunction, metabolic disorders
- Open questions
  - What should be the goal for these pts?
    - Maximal response versus disease stabilization
    - 'One size fits all' no longer applies
  - Which regimens and for how long?

[1]Ludwig et al. JCO 2010; 28: 1599-605
[2]Brenner et al. Blood 2008; 111: 2521-2526

Expanding treatment options in front-line therapy for elderly myeloma pts

MP + novel agents

- **VMP** (VISTA, PETHEMA, GIMEMA)
- **VMPT-VT** (GIMEMA)
- **VMP-VT/VP** (PETHEMA)
- **MPT** (GIMEMA, IFM, NMSG, HOVON, Turkish study group)
- **MPR-R** (GIMEMA)

Dex + novel agents

- **Bortezomib/Dex-based** (UPFRONT study)
- Including VTD
- **Thal/Dex-based** (ECOG, Celgene 003, CEMSG, MRC Myeloma IX)
- **Len/Dex** (ECOG, SWOG others)
- **Len/Bortezomib/Dex** (DFCI)

Thalidomide-based treatment for elderly pts with newly diagnosed MM

- MPT vs MP (6 randomized phase III trials)[1-6]
  - 4/6 studies: PFS benefit
  - 3/6 studies: OS benefit
  - Meta-analyses and systematic review[7-9]
    - MPT superior to MP for ORR, CR, PFS, EFS: not OS
- CTDa vs MP (phase III MRC Myeloma IX trial)[10,11]
  - CTDa superior for ORR and CR: not PFS or OS
  - Thal maintenance increased PFS: not OS
- Thal/Dex vs MP (phase III trial)[12,13]
  - Thal/dex superior for ORR and ≥VGPR: not PFS or OS
  - Thal/IFN maintenance improved PFS: not OS over IFN

[1]Palumbo et al. Blood 2008; 112: 3107-3114
[2]Facon et al. Lancet 2007; 370: 1209-1218
[3]Hulin et al. J Clin Oncol 2009; 27: 3664-70
[4]Waage et al. Blood 2010; 116: 1405-12
[5]Wijermans et al. J Clin Oncol 2010; 28: 3160-6
[6]Beksac et al. Eur J Haematol 2011; 86: 16-22
[7]Waage et al. ASCO 2010 (abstract 8130); EHA 2010 (abstract 567)
[8]Kumar et al. Am J Hematol 2011; 86: 18-24
[9]Kapoor et al. Leukemia 2011 Jan 14 [Epub]
[10]Morgan et al. ASH 2009 (abstract 352), oral presentation
[11]Morgan et al. ASH 2010 (abstract 623), oral presentation
[12]Ludwig et al. Blood 2009; 113: 3435–3442
[13]Ludwig et al. Haematologica 2010; 95: 1548-1554

Lenalidomide-based treatment for elderly pts with newly diagnosed MM

- **Phase III MM-015 study: MPR-R versus MPR versus MP[1]**
  - **All pts**
    - **MPR-R superior to MP for PFS (31 vs 13 mos)**
    - **MPR and MP comparable PFS (14 vs 13 mos)**
    - **No difference in OS between arms**
  - **Pts 65-75 yrs**
    - **MPR-R superior to MPR and MP for PFS (not reached vs 14.7 mos vs 12.4 mos)**
- **Phase III ECOG trial: RD vs Rd[2]**
  - **Rd superior to RD for PFS and OS regardless of age group**
  - **RD associated with higher rate of toxicity**
- **Phase I/II: RVD[3]**
  - **Phase I/II trial included elderly pts**
- **Phase III: MM-020 Rd vs MPT (ongoing)**

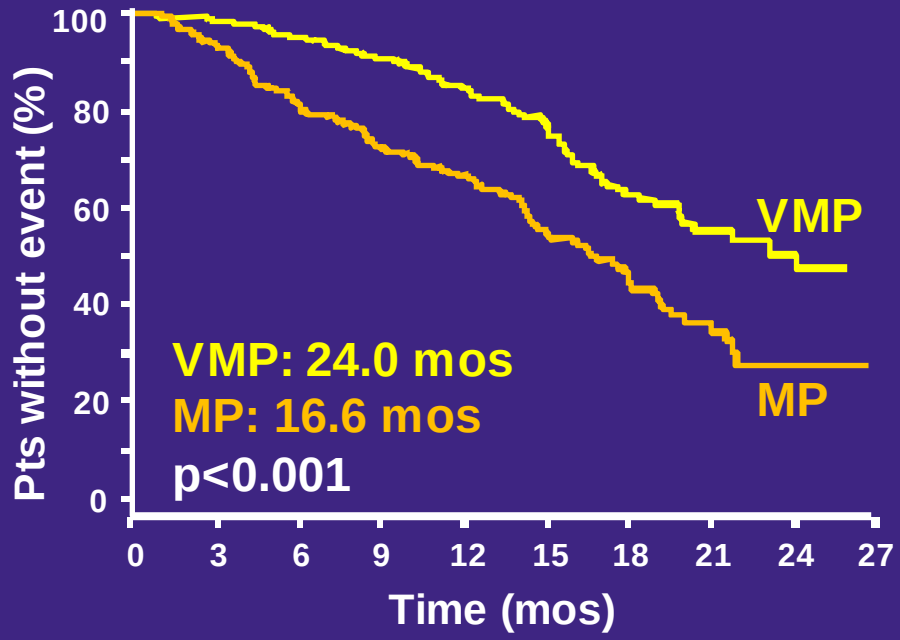
[1]Palumbo et al. ASH 2010 (Abstract 622), oral presentation
[2]Vesole et al. ASH 2010 (Abstract 308), oral presentation
[3]Richardson et al. Blood 2010; 116(5): 679-686

Phase III VISTA trial: VMP vs MP

Response rates

	VMP	MP	p
ORR	71%	35%	<0.001
CR	30%	4%	<0.001

Time to progression (primary endpoint)

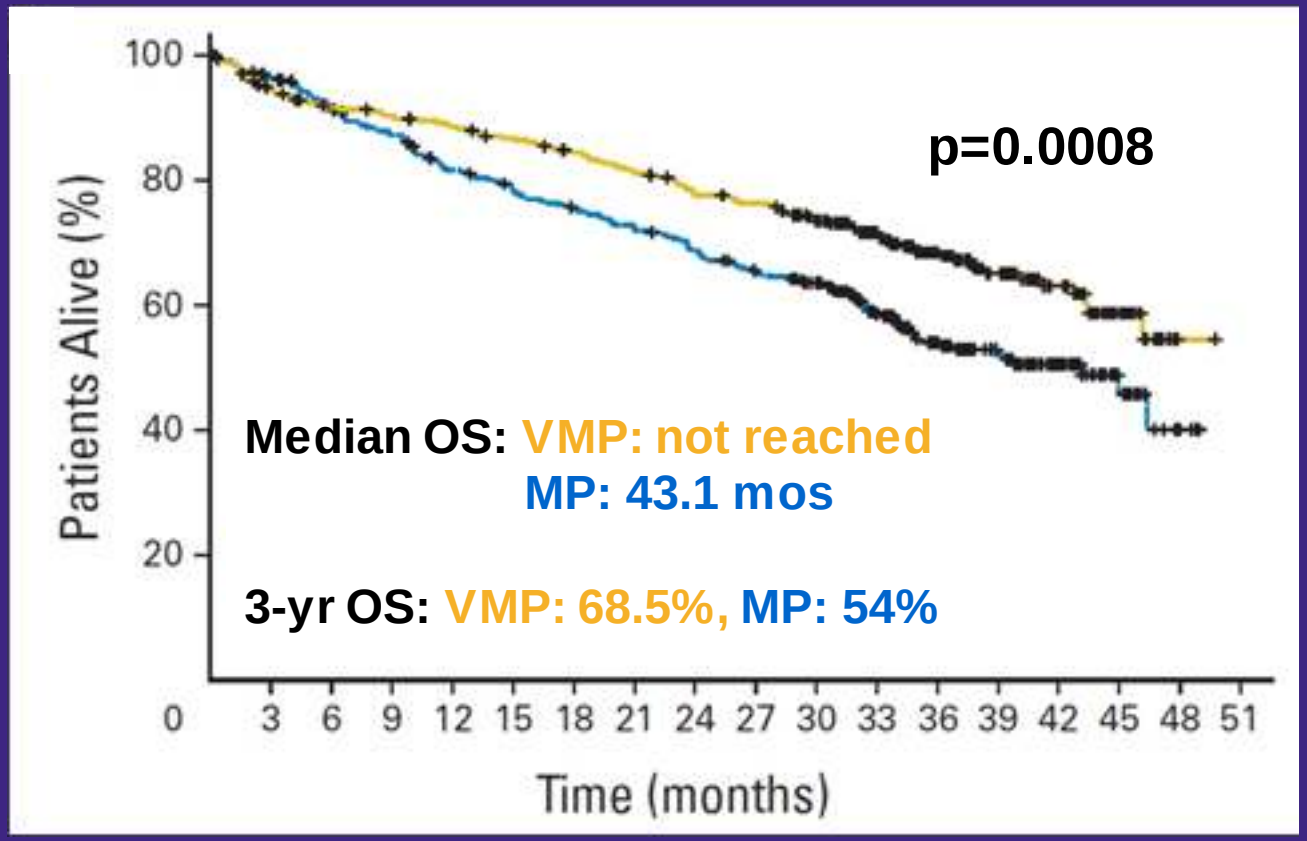


VMP superior to MP regarding ORR, CR and TTP

Adapted from: San Miguel et al. N Engl J Med 2008; 359(9): 906-917

VISTA: Overall survival

Median follow-up 36.7 mos



Overall survival benefit for VMP versus MP despite 50% of MP pts receiving bortezomib upon progression

Adapted from: Mateos et al. J Clin Oncol 2010; 28(13): 2259-2266

VISTA: Subsequent therapies

178 (52%) VMP and 233 (69%) MP pts have received subsequent therapy

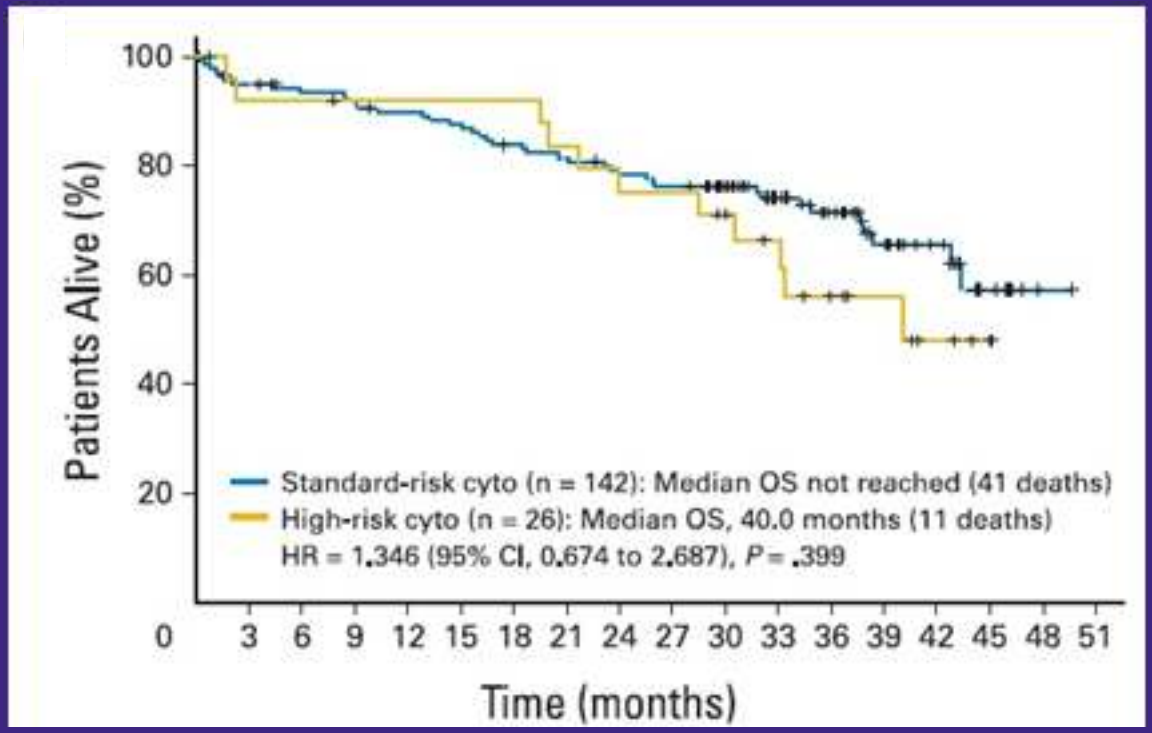
Subsequent therapy and responses achieved		VMP (n=178)	MP (n=233)
Bortezomib-based therapy	Retreatment	n=43	n=116
≥PR		47%	59%
Thalidomide-based therapy		n=81	n=110
≥PR		41%	53%
Lenalidomide-based therapy		n=57	n=30
≥PR		59%	52%

Pts can be successfully treated with subsequent IMiD-based therapy and can also be retreated with bortezomib

Adapted from: Mateos et al. J Clin Oncol 2010; 28(13): 2259-2266

VISTA subgroup analyses in VMP arm: Cytogenetics

Overall survival according to cytogenetics



- No difference in OS between pts with standard-risk vs high-risk cytogenetics
- Trend to longer OS in pts with standard-risk cytogenetics

Mateos et al. J Clin Oncol 2010; 28(13): 2259-2266

VISTA subanalysis: Renal impairment

	VMP		MP	
GFR (mL/min)	≤50	>50	≤50	>50
CR+PR (%)	68	72	46	29
CR (%)	31	30	5	3
Median time to first response (mos)	1.0	1.4	3.4	4.9
Median duration of response (mos)	16.9	22.4	12.9	20.5
TTP (mos)	19.9	NE	16.1	18.0
3-yr OS (%)	60.7	76.9	41.5	67.9
Discontinuation due to AE (%)	16	14	18	12
Dose reduction due to AEs (%)				
Bortezomib (%)	50	48	-	-
Second bortezomib reduction (%)	16	19	-	-
Melphalan (%)	23	10	17	11

- Renal impairment reversal: VMP 44%, MP 34%
- In both arms: rates of Gr 4 & 5 AEs & SAEs appeared higher in pts with renal impairment

VMP is a feasible, active, and generally well-tolerated treatment option for previously untreated pts with MM with moderate renal impairment

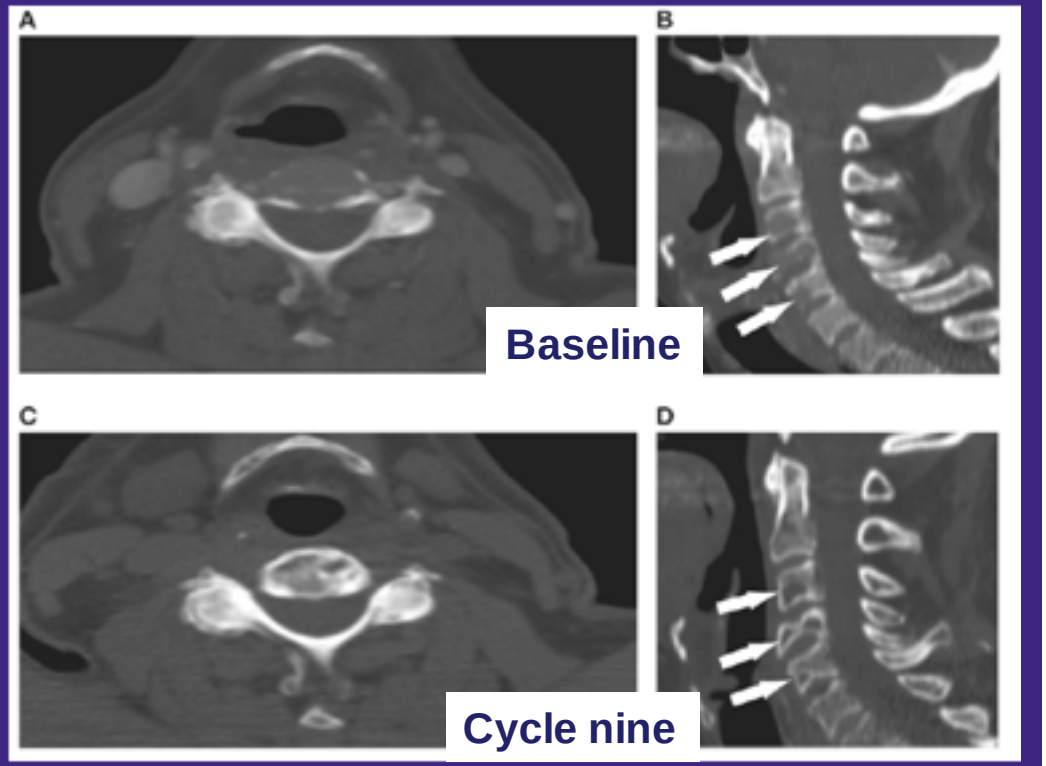
Adapted from: Dimopoulos et al. JCO 2009; 27(36): 6086–6093

VISTA subanalysis: Bone disease

- VMP versus MP:
  - Lower rates of bisphosphonate use
  - Lower rate of progression due to worsening bone disease
  - Lower requirement for subsequent radiotherapy
- Bone healing in 6 pts receiving VMP (out of 11 pts with pre- and post-baseline radiologic data)

CT scans for pt with CR to VMP

C4 **Cervical spine**



Delforge et al. Eur J Haematol 2011 Mar 2 [Epub ahead of print]

VISTA: Adverse events
(occurring in ≥ 5% of pts)

	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
Leukopenia	21	3	16	4
Lymphopenia	14	6	9	2
Peripheral sensory neuropathy	13	<1	0	0
Neuralgia	8	1	<1	0
Fatigue	7	1	2	0
Diarrhea	7	1	1	0
Pneumonia	5	2	4	1
Hypokalemia	6	1	2	1
Asthenia	6	<1	3	0

Mateos et al. J Clin Oncol 2010; 28(13): 2259-2266

Summary: VISTA

- VMP is superior to MP for ORR, CR, TTP[1]
- VMP prolongs OS versus MP[2]
- Retreatment with bortezomib-based therapy after VMP is effective[2]
- Subgroup analyses in VMP arm
  - Comparable OS between pts with standard-risk and high-risk cytogenetics[2]
  - Active and manageable toxicity in pts with moderate renal impairment; reversal of renal impairment in 44%[3]

[1]San Miguel et al. N Engl J Med 2008; 359(9): 906-917
[2]Mateos et al. J Clin Oncol 2010; 28(13): 2259-2266
[3]Dimopoulos et al. JCO 2009; 27(36): 6086-6093

Improving on VMP

- Add a 4th drug: VMPT[1]
- Change the combination: VTP[2]
- Include maintenance treatment: VT, VP[2]
- Investigate once-weekly administration of bortezomib[1,2]
- Evaluate subcutaneous administration of bortezomib[3]
- Evaluate novel combinations with bortezomib (e.g. lenalidomide)[4]

[1]Palumbo et al. ASH 2010 (Abstract 620), oral presentation
[2]Mateos et al. Lancet Oncol 2010; 11(10): 934-941
[3]Moreau et al. Lancet Oncol 2011 [Epub ahead of print]
[4]Richardson et al. Blood 2010; 116: 679-686

Phase III: VMPT-VT vs VMP in newly diagnosed elderly pts (GIMEMA)

- **Pts** (n=511): >65 yrs old; median age 71 yrs

VMPT + VT

9 x 5-wk cycles:*
Bortezomib 1.3 mg/m^2, d 1,8,15,22
Melphalan 9 mg/m^2 d 1-4
Prednisone 60 mg/m^2 d 1-4
Thalidomide 50 mg/d continuously

↓

Maintenance (until relapse):
Bortezomib 1.3 mg/m^2 d 1, 15
Thalidomide 50 mg continuously

VMP

9 x 5-wk cycles:*
Bortezomib 1.3 mg/m^2, d 1,8,15,22
Melphalan 9 mg/m^2 d 1-4
Prednisone 60 mg/m^2 d 1-4

↓

No maintenance

*Protocol amendment: from twice-wkly bortezomib dosing (d 1,4,8,11,22,25,29,32) to once-wkly bortezomib dosing (d 1,8,15,22);

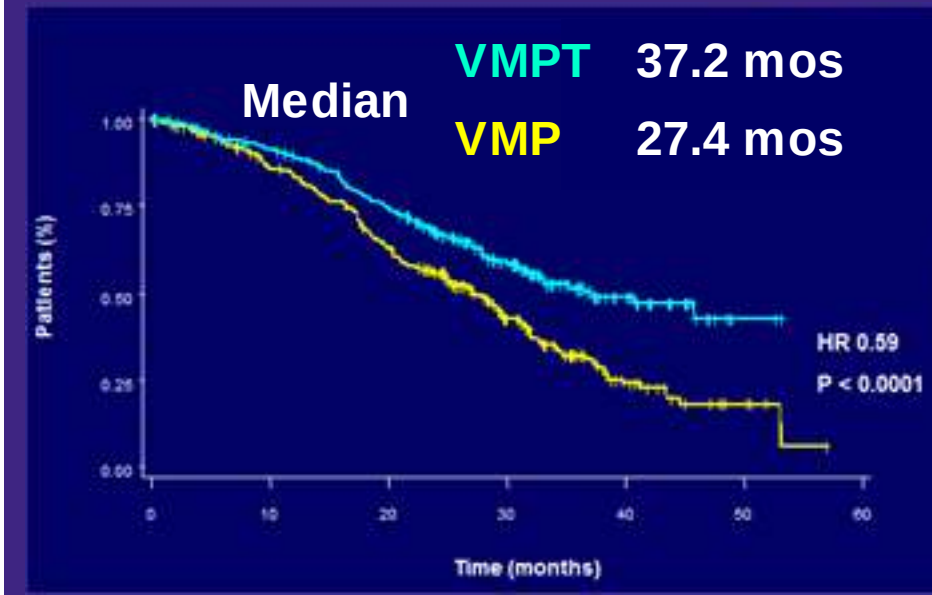
61 pts in VMP arm and 70 pts in VMPT arm received twice-wkly bortezomib dosing.

Palumbo et al. ASH 2010 (Abstract 620), oral presentation
Palumbo et al. J Clin Oncol 2010; 28: 5101-5109

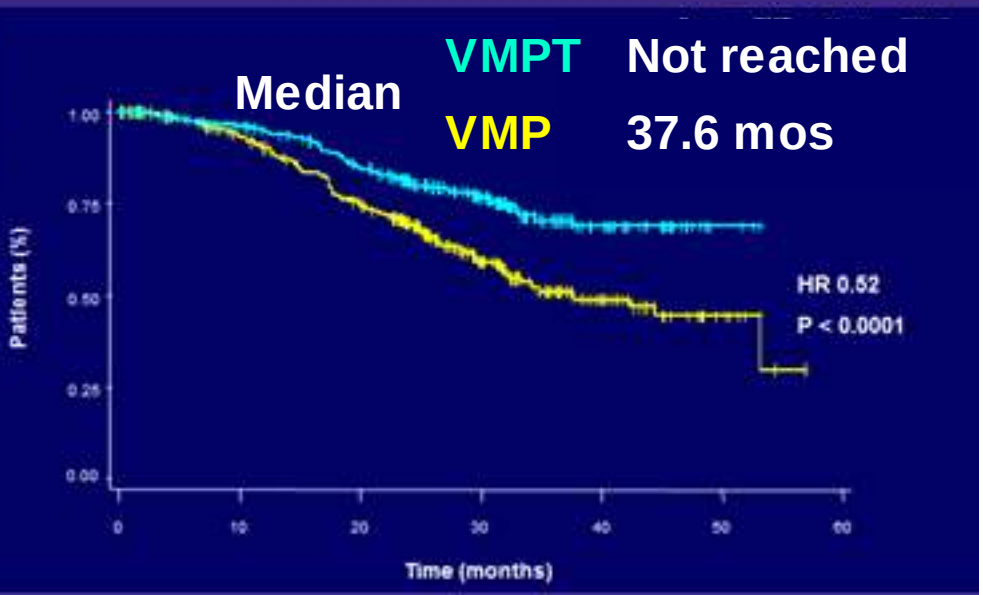
Efficacy data

Median follow up: 32 mos

PFS



TTNT



Landmark analysis after 9 cycles demonstrates impact of maintenance treatment:

52% reduced risk of progression with VMPT-VT (HR 0.48, p<0.0001)

Palumbo et al. ASH 2010 (Abstract 620), oral presentation

Adverse events and treatment discontinuation

Grade 3/4 Adverse events

	VMPT-VT	VMP
Neutropenia	38%	28%
Thrombocytopenia	22%	20%
Anemia	10%	10%
PN	8%	5%
Infections	13%	9%
Cardiologic	10%	6%
DVT/PE	5%	2%

Treatment discontinuation

	VMPT-VT	VMP
Discontinuation rate due to AEs		
65-75 yrs	27%	16%
>75 yrs	37%	18%
Median cumulative bortezomib dose		
65-75 yrs	61mg/m^2	42mg/m^2
>75 yrs	31mg/m^2	37mg/m^2

Greatest benefit for VMPT-VT in pts 65-75 yrs old

Palumbo et al. ASH 2010 (Abstract 620), oral presentation

Summary

- Addition of 4th drug + maintenance (VMPT-VT) improves PFS compared to VMP in pts <75 yrs old
- Reduced-intensity bortezomib dosing improves tolerability (compared to VISTA)
- Toxicity of Thal in elderly remains a challenge
- Validation of combination approach of novel therapies in the elderly

Palumbo et al. ASH 2010 (Abstract 620), oral presentation

Phase III: VMP vs VTP in newly diagnosed elderly pts with MM (PETHEMA/GEM study)

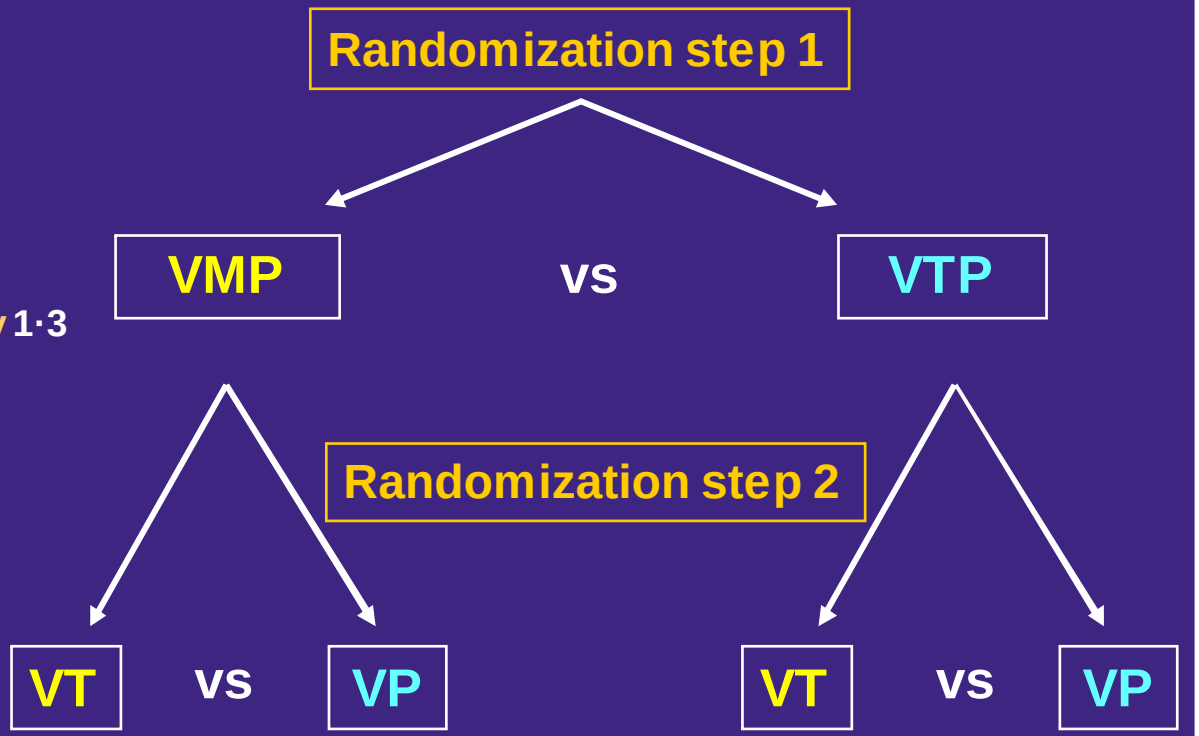
- Pts (n=260), ≥65 yrs old (median age 73 yrs)
- Multicenter, two-stage randomized trial

Induction (6 cycles)

- One 6-wk cycle, bortezomib 2x wkly
1·3 mg/m² d 1,4,8,11,22,25,29,32
+ Mel 9 mg/m² d 1–4 or Thal 100 mg/d
+ Pred 60 mg/m² d 1–4
- Five 5-wk cycles, bortezomib 1x wkly 1·3 mg/m² d 1,8,15,22
+ same doses of mel or thal and pred

Maintenance (up to 3 yrs)

Bortezomib: 1.3 mg/m² d 1, 4, 8, 11
every 3 mos
+ Thal 50 mg/d
or Pred 50 mg alternate days



Mateos et al. Lancet Oncol 2010; 11(10): 934-941

Response data

Response to induction	VMP (n=130)	VTP (n=130)
ORR	80%	81%
CR IF-	20%	28%
CR IF+	12%	8%
PR	48%	45%
Response to maintenance therapy	**VT (n=91)**	**VP (n=87)**
CR IF-	44%	39%

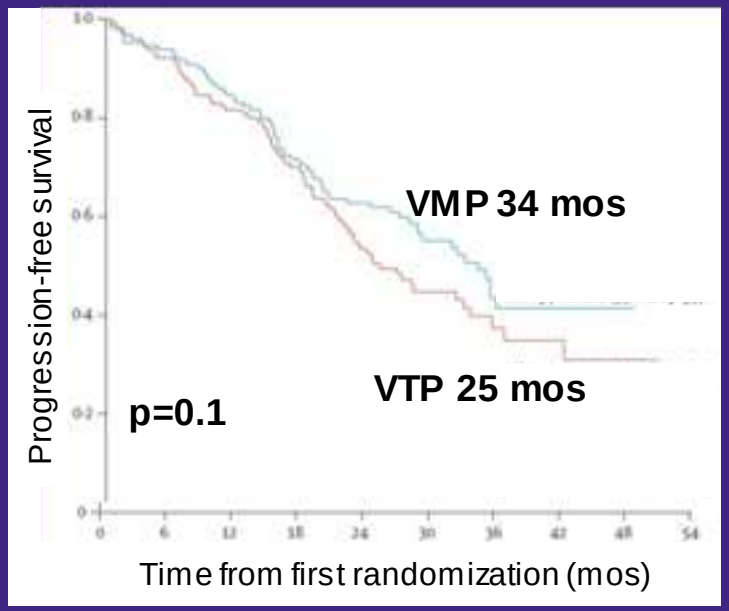
- Comparable efficacy with VMP and VTP
- Both maintenance regimens increased CR rate

Adapted from: Mateos et al. Lancet Oncol 2010; 11(10): 934-941

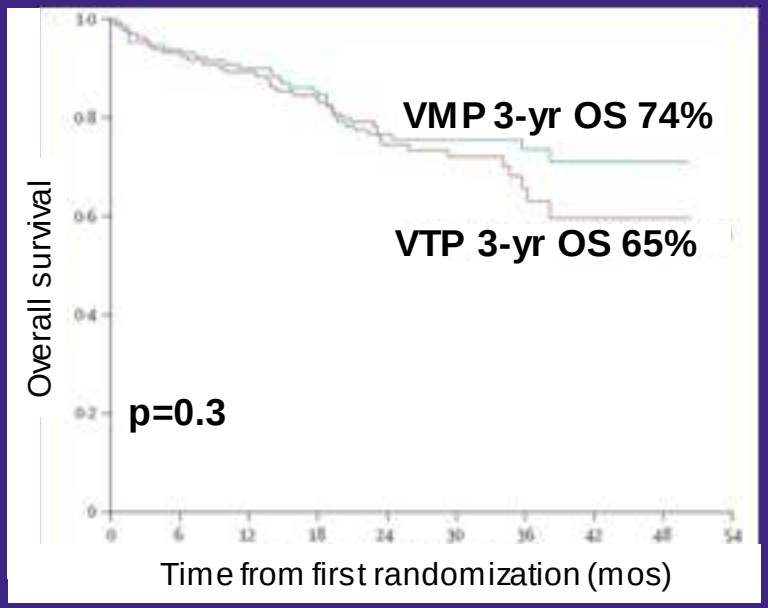
PFS and OS

- No significant difference in PFS and OS between VMP and VTP groups

PFS



OS



- No significant difference in PFS and OS between VT or VP maintenance
  - PFS: VT 32 mos, VP 24 mos, p=0.1
  - OS: HR 1.2, 0.6–2.4

Adapted from: Mateos et al. Lancet Oncol 2010; 11(10): 934-941

Efficacy, PFS, OS according to cytogenetic abnormalities

- **High-risk:** t(4;14) ± t(14;16) ± del(17p)
- **Standard-risk:** Absence of t(4;14), t(14;16), del(17p)

	Standard-risk (n=187)	High risk (n=44)	p
CR after induction	26%	26%	n/a
CR after maintenance	45%	39%	n/a
PFS first randomization	33 mos	24 mos	0.01
PFS second randomization	27 mos	17 mos	0.01
3-yr OS from first randomization	77%	55%	0.001
3-yr OS from second randomization	85%	60%	<0.0001

Adapted from: Mateos et al. Lancet Oncol 2010; 11(10): 934-941

Adverse events

Toxicity profile: induction

≥Gr 3 Adverse events	VMP (n=130)	VTP (n=130)	p
Anemia	12%	8%	0.7
Neutropenia	39%	22%	0.008
Thrombocytopenia	27%	12%	0.0001
Cardiac events	0	8%	0.001
Infections	7%	1%	0.01
DVT / TE	1%	2%	0.5
PN	7%	9%	0.6
GI toxicitiy	7%	2%	0.2
SAEs	15%	31%	0.01
Discontinuation due to SAEs	12%	17%	0.03
Deaths	5%	5%	0.8

Toxicity profile: maintenance

≥Gr 3 Adverse events	VP*	VT*
Anemia	3%	4%
Neutropenia	1%	2%
Thrombocytopenia	1%	1%
GI toxicities	1%	4%
PN	2%	7%
Infections	2%	2%
DVT / TE	0	1%
Cardiac events	1%	2%
Discontinuation due to AEs	5%	8%
Deaths	1%	1%

*No significant difference in incidences between arms

More SAEs and discontinuations with VTP

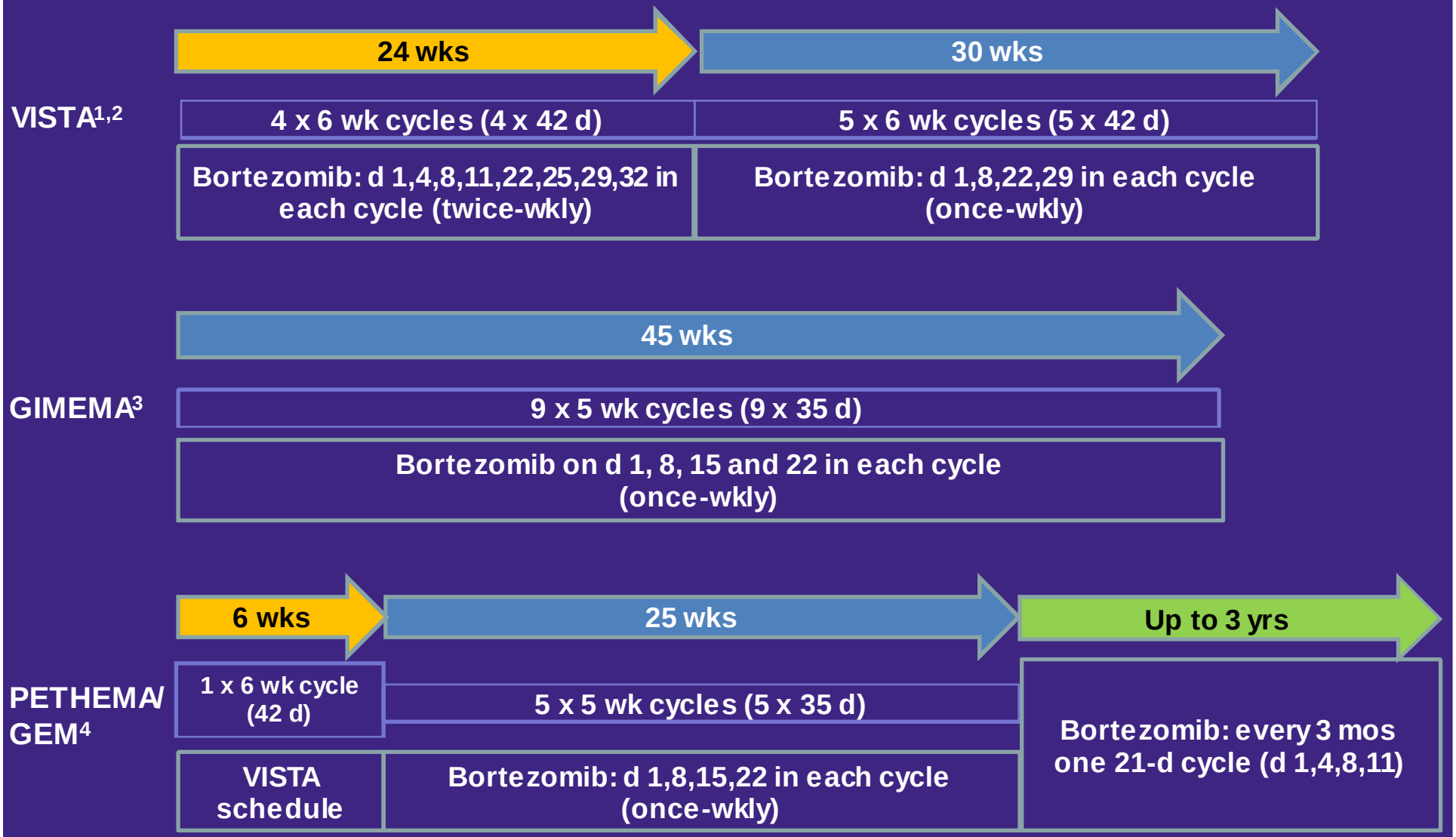
Adapted from: Mateos et al. Lancet Oncol 2010; 11(10): 934-941

Summary

- Addition of maintenance (VT or VP) improves PFS
- Reduced-intensity bortezomib dosing followed by maintenance improves tolerability (compared to VISTA)
- VMP better tolerated than VTP for non-hematological toxicity
- VMP followed by VT:
  - Preferred approach?
  - Optimal wkly bortezomib schedule in induction (esp. high-risk); in maintenance (q 3mos vs q 2wks)?

Mateos et al. Lancet Oncol 2010; 11(10): 934-941

Overview of VMP schedules in phase III trials



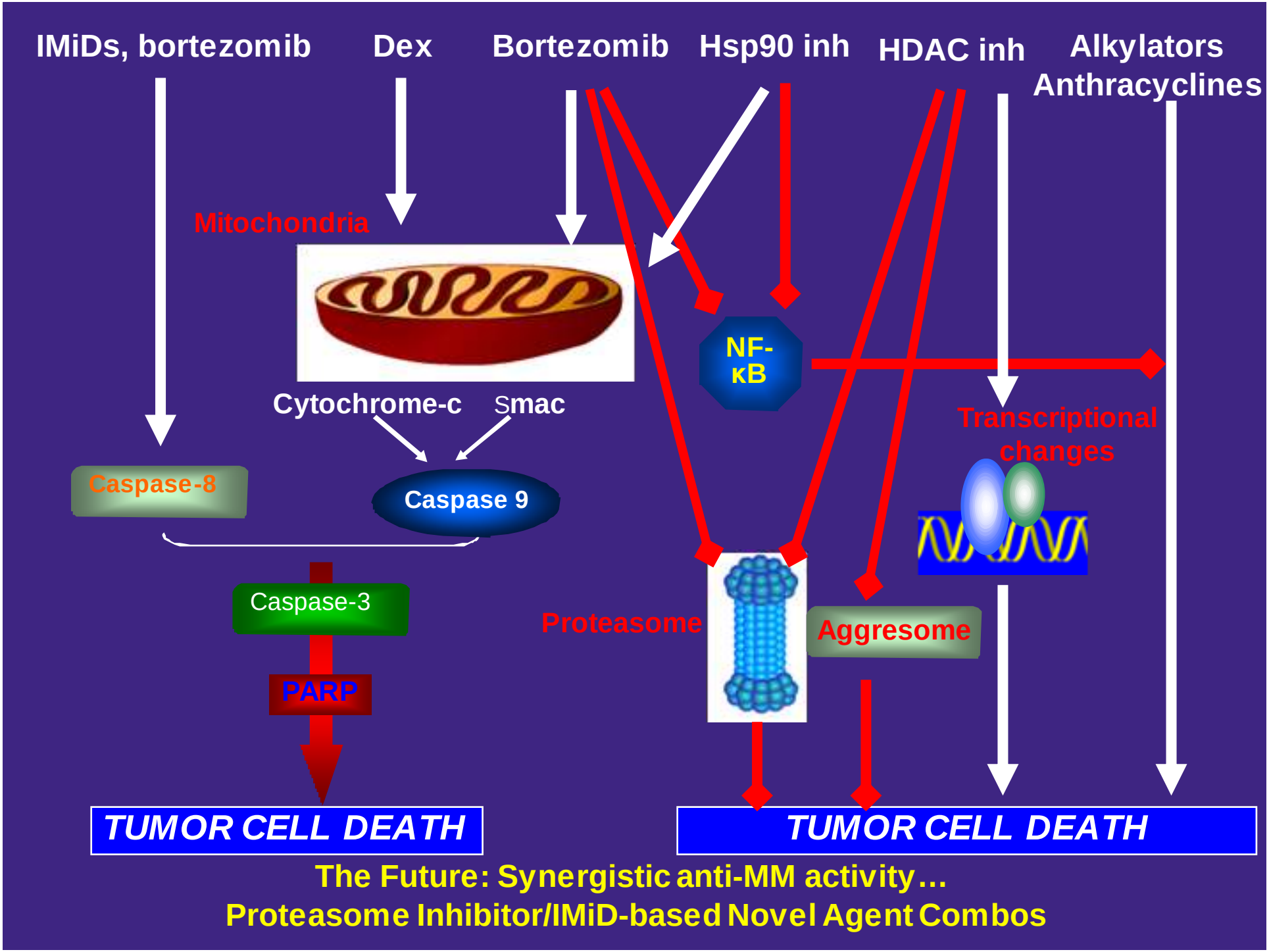
[1]San Miguel et al. NEJM 2008; 359: 906-917
[2]Mateos et al. J Clin Oncol 2010; 28: 2259-2266
[3]Palumbo et al. J Clin Oncol 2010; 28: 5101-5109
[4]Mateos et al. Lancet Oncol 2010; 11: 934-941

Flexible dosing: Comparable efficacy with improved tolerability

Study details	Efficacy				Sensory PN		Discont. due to PN	Discont. due to AEs overall
	ORR	CR	Median PFS	3-yr OS	All grades	Grade 3/4		
VMP with twice-wkly bortezomib administration								
VISTA[1-3]	71%	30%	21.7m	68.5%	44%	13%	15%	34%
VMP with once-wkly bortezomib administration								
GIMEMA[4,5]	79%	23%	27m	87%	22%	2%	4%	17%
PETHEMA/GEM[6]	80%	20%	34m	74%	NR	7%	NR	12%†

†Discontinuations due to SAEs

1. San Miguel et al. NEJM 2008; 359: 906-917
2. San Miguel et al. NEJM 2008; 359: 906; Suppl. App.
3. Mateos et al. J Clin Oncol 2010; 28: 2259-2266
4. Palumbo et al. J Clin Oncol 2010; 28: 5101-5109
5. Bringhen et al. Blood 2010; 116: 4745-4753
6. Mateos et al. Lancet Oncol 2010; 11: 934-941


IMiDs, bortezomib
Dex
Bortezomib
Hsp90 inh
HDAC inh
Alkylators
Anthracyclines
Mitochondria
Cytochrome-c
Smac
NF-κB
Transcriptional changes
Caspase-8
Caspase 9
Caspase-3
PARP
Proteasome
Aggresome
TUMOR CELL DEATH
TUMOR CELL DEATH
The Future: Synergistic anti-MM activity…
Proteasome Inhibitor/IMiD-based Novel Agent Combos

Phase I/II: Lenalidomide, bortezomib, dex (RVD) in newly diagnosed MM

- **Treatment**
  - 8 x 3-wk cycles: Lenalidomide, bortezomib, dex then maintenance (ASCT optional)
- **Results**
  - N=66 (median age 58 yrs, range 22-86)
  - MTD Len 25 mgs; Bortezomib 1.3 mg/m^2; dex 20 mgs
  - Best response to treatment (median 10 cycles of treatment):

	All pts (n=66)	Phase 2 population (n=35)
CR	29%	37%
≥nCR	39%	57%
≥VGPR	67%	74%
≥PR	100%	100%

  - Median follow-up: 21 mos
    - Median PFS & OS not reached
    - 18-mos PFS 75%
    - 18-mos OS 97%
  - Most common AEs:
    - Sensory PN, fatigue, constipation
    - Gr 3 PN: 7% (no Gr 4 PN)
    - Overall rate of DVT/PE: 6%
    - No treatment-related mortality

Richardson et al. Blood 2010;116:679-686

Conclusions/Future Directions:

- **Three large phase III trials demonstrate substantial efficacy of VMP and VMP-based regimens[1,2,5,6]**
  - **VISTA[1,2]**
    - **Unprecedented CR rates, improvement in TTP, PFS and OS compared to MP[1,2]**
    - **Efficacy in specific subgroups: cytogenetic abnormalities, renal impairment, positive impact on bone disease[2,3,4]**
  - **GIMEMA & PETHEMA trials[5,6]**
    - **Prolonged treatment / addition of maintenance therapy associated with PFS benefit**
    - **Weekly bortezomib (Bz) dosing improves tolerability**
- **Newer combinations: bortezomib/lenalidomide based (RVD "lite")**
- **Future directions: SubQ, weekly administration of Bz, addition of other novel agents (eg second generation PIs, HDAC inhibitors, other small molecules, 3rd generation IMiDs, MoAbs)**

[1]San Miguel et al. N Engl J Med 2008; 359(9): 906-917
[2]Mateos et al. J Clin Oncol 2010; 28(13): 2259-2266
[3]Dimopoulos et al. JCO 2009; 27(36): 6086-6093
[4]Delforge et al. Eur J Haematol 2011 Mar 2 [Epub ahead of print]
[5]Palumbo et al. ASH 2010 (Abstract 620), oral presentation
[6]Mateos et al. Lancet Oncol 2010; 11(10): 934-941

Future Directions (Continued)

- Tailored approach to therapy:
  - Identify groups of pts in whom combinations are required versus pts in whom doublets and/or sequences should be used
  - Use of GEP, Proteomics
  - Risk adaptation

Clinical Investigators in MM - A Global Network: Leadership, including Anderson KC., Harousseau JL., San Miguel J., Kyle R., Facon T., Boccadoro M., Blade J.

VISTA/ APEX/ SUMMIT/CREST/009/010/015/020 Combination Studies Investigators

Sponsors including Millenium; Celgene; J & J; Novartis; BMS; Keryx; Merck

ECOG, CALGB, MMRC, GIMEMA, IFM, PETHEMA/GEM, Nordic SG

Advocacy/Support MMRF; IMF ; FDA; EMEA

Abubakr Y.
Agura E.
Alexanian R.
Alsina M.
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Attal M.
Avigan D.
Barlogie B.
Baccarani M.
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Moreau P.
Landau H.
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Palumbo, A.
Munshi, N.

Cavenagh J.
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Giralt S.
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Goldschmidt H.
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Hassoun H.
Hegewisch-Becker C.
Hideshima T.
Huber C.
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Hussein M.
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Irwin D.
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Mavromatis B.
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Morris C.
Morrison V.
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Nowrousian M.
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Rahemtulla A.
Rai K.
Rajkumar V.

Reece D.
Richardson P.
Rowe J.M.
Schilder R.
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Schuster M.
Sezer O.
Shadduck R.
Shustik C.
Siegel D.
Singhal S.
Sonneveld P.
Sotto J.J.
Stadtmauer E.
Stewart, K
Tarantolo S.
Van Droogenbroeck V.
Van Oers M.H.
Vellenga E.
Vesole D.
Vij R.
Wang M.
Zachee P.
Zangari M.
Zeldenrust, S
Zonder, J


Optimizing Patient Outcomes Through Individualized Treatment Approaches: Phase III Data
Co-Chairs: Robert Orlowski, USA and
Pieter Sonneveld, The Netherlands
Med/MMa/FEB2011/EMEA045

The impact of proteasome inhibition in the transplant setting

Pieter Sonneveld

Med/MMa/FEB2011/EMEA045

Improving outcomes in ASCT eligible patients with novel agents

Goals of incorporating novel agents in induction and post-transplant regimens

- **Induction**
  - **Improve CR rates pre-transplant**
    - **Association between depth of response and OS with novel agents seen in a number of studies[1-4]**
- **Post-transplant therapy**
  - **Consolidation: improve depth of response**
  - **Maintenance: maintain response**

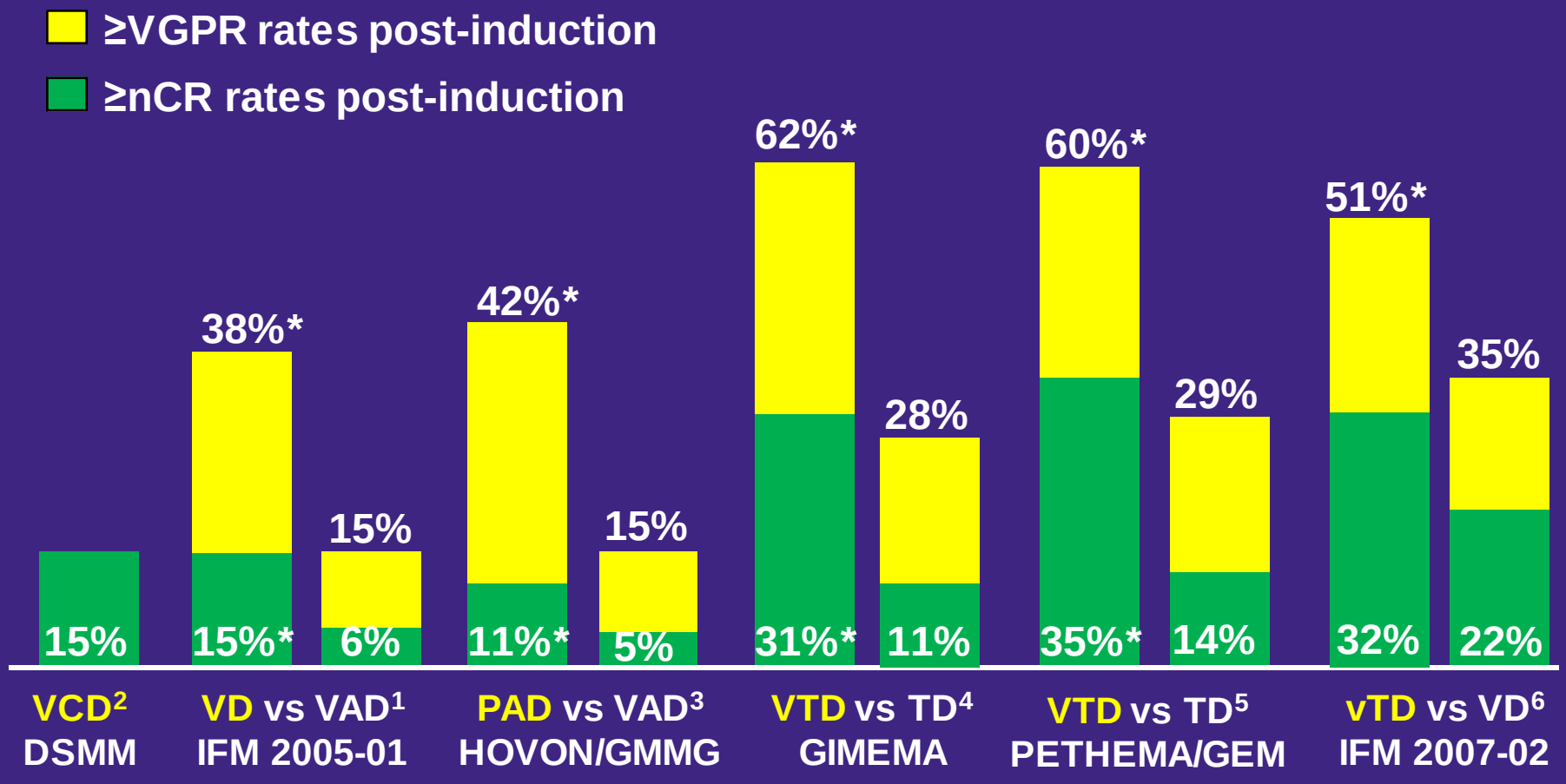
[1]Morgan et al. Blood 2009; 114(22); Abstract 352 (oral presentation)
[2]Morgan et al. Clin. Lymphoma & Myeloma 2009; 9 (suppl 1): Abstract A546 (oral presentation)
[3]Moreau et al. Blood 2011; 117(11): 3041-3044
[4]Cavo et al. Lancet 2010; 376(9758): 2075-2085

Bortezomib as part of induction regimens

- **Bortezomib/dex (IFM 2005/01 trial)**
  - **Bortezomib/dex induction superior to VAD[1]**
    - **Significantly higher ≥nCR and ≥VGPR rates post-induction and post-transplant**
    - **Superior PFS**
    - **Prolonged 3-year OS**
  - **Bortezomib/dex could be considered the backbone of induction regimens before high-dose therapy[2]**
- **Combinations based on bortezomib/dex**
  - **VCD, PAD, VTD, VTDC, VRD**

[1]Harousseau et al. J Clin Oncol 2010;28(30):4621-4629
[2]Moreau et al. Leukemia 2010;24(6):1233-1235

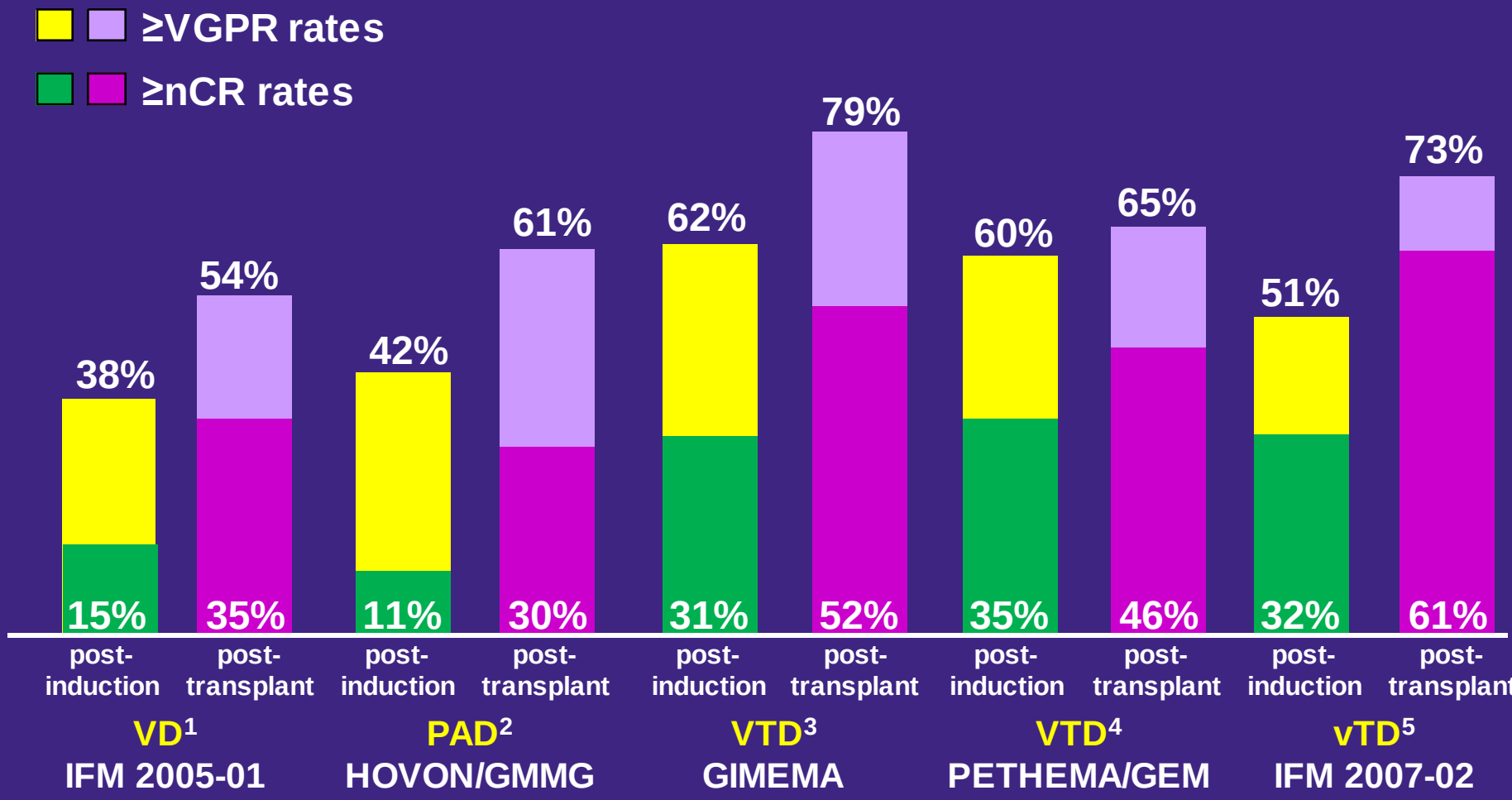
Significant improvement in post-induction CR/nCR and VGPR rates with bortezomib-based induction regimens



***significant difference between arms**

[1]*Harousseau et al. J Clin Oncol 2010; 28(30): 4621-4629*
[2]*Einsele et al. Blood 2009; 114(22); Abstract 131 (oral presentation)*
[3]*Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)*
[4]*Cavo et al. Lancet 2010; 376(9758): 2075-2085*
[5]*Rosinol et al. Blood 2010; 116(21); Abstract 307 (oral presentation)*
[6]*Moreau et al. J Clin Oncol 2010; 28(15 suppl): Abstract 8014 (oral presentation)*

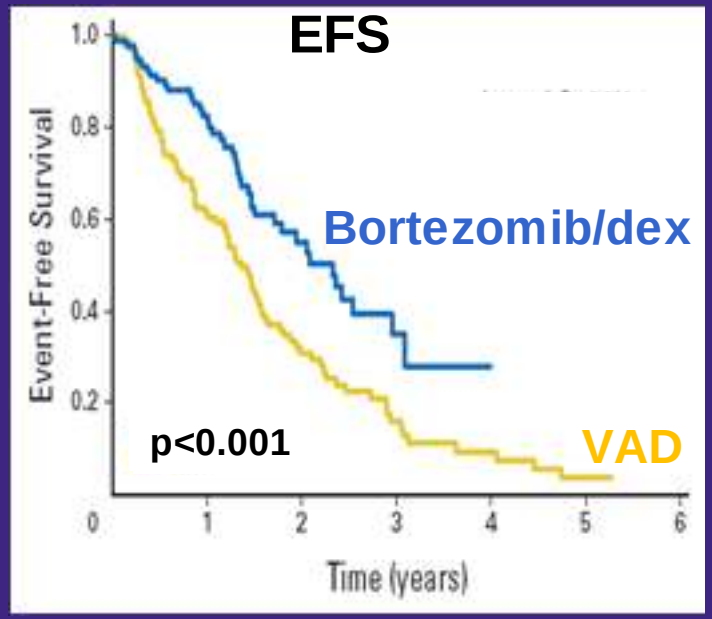
Significant improvement in post-induction and post-transplant CR/nCR and VGPR rates with bortezomib-based induction regimens

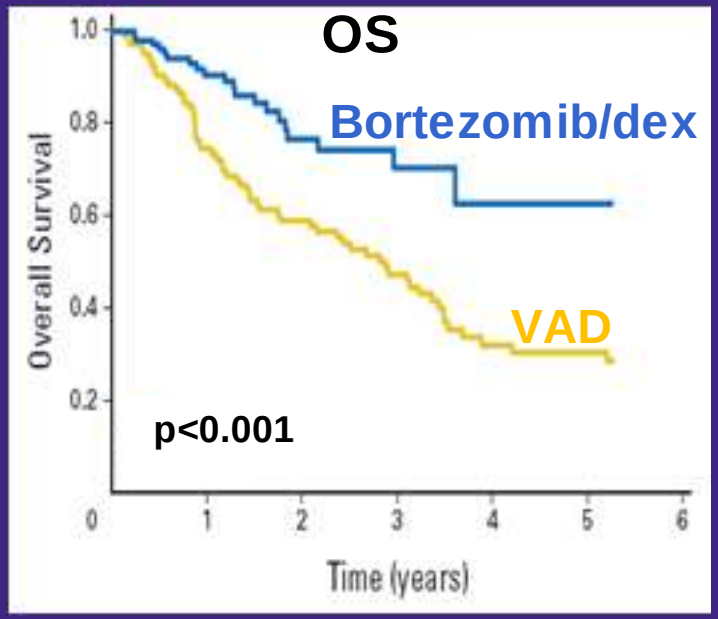


[1]*Harousseau et al. J Clin Oncol 2010; 28(30): 4621-4629*
[2]*Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)*
[3]*Cavo et al. Lancet 2010; 376(9758): 2075-2085*
[4]*Rosinol et al. Blood 2010; 116(21); Abstract 307 (oral presentation)*
[5]*Moreau et al. J Clin Oncol 2010; 28(15 suppl): Abstract 8014 (oral presentation)*

Bortezomib regimens in the presence of cytogenetic abnormalities

Impact of t(4:14) in phase III IFM 2005/01 trial: Bortezomib/dex vs VAD[1]





For del(17p):

- **Bortezomib/dex does not improve outcome[1]**
- **Bortezomib partly overcomes poor risk conferred by del(17p)[2,3]**

Other trials support cytogenetics data[4-6]

[1]*Avet-Loiseau et al. J Clin Oncol 2010;28:4630-4634*
[2]*Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)*
[3]*Neben K et al. Blood 2010;116(21); Abstract 305 (oral presentation)*
[4]*Cavo et al. Lancet 2010; 376(9758): 2075-2085*
[5]*Rosinol et al. Blood 2010; 116(21); Abstract 307 (oral presentation)*
[6]*Einsele et al. Blood 2009; 114(22); Abstract 131 (oral presentation)*

Summary: Induction

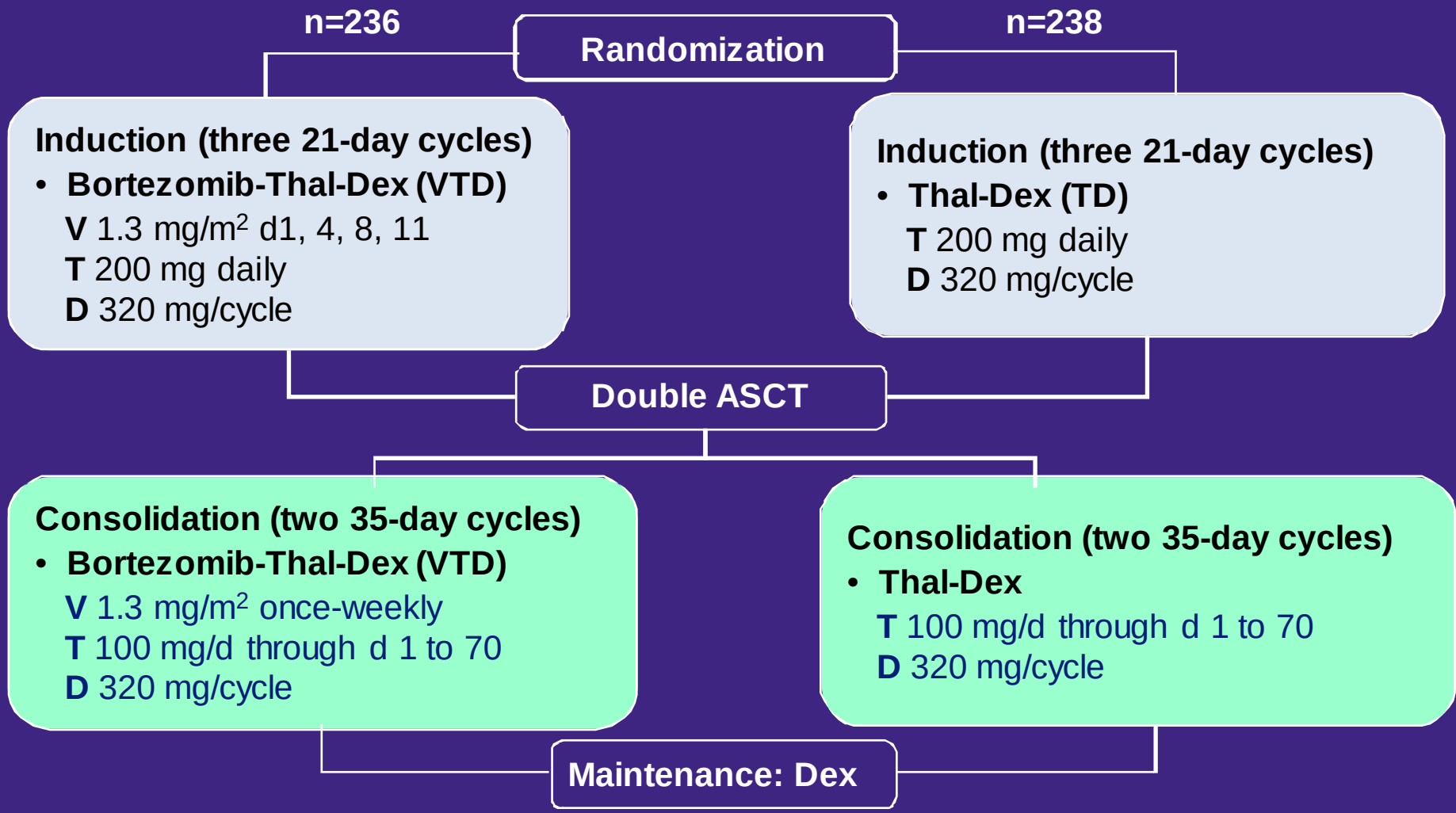
- **Aim of induction: achieve high CR rate prior to transplant**

- **Effective three-drug regimens based on bortezomib/dex backbone: VCD, PAD, VTD**
  - **Significant improvements in CR/nCR rates post-induction and post-transplant[1-6]**
  - **Efficacy improved compared to conventional regimens in the presence of some high-risk cytogenetic features[1-7]**

[1]*Harousseau et al. J Clin Oncol 2010; 28(30): 4621-4629*
[2]*Einsele et al. Blood 2009; 114(22); Abstract 131 (oral presentation)*
[3]*Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)*
[4]*Cavo et al. Lancet 2010; 376(9758): 2075-2085*
[5]*Rosinol et al. Blood 2010; 116(21); Abstract 307 (oral presentation)*
[6]*Moreau et al. J Clin Oncol 2010; 28(15 suppl): Abstract 8014 (oral presentation)*
[7]*Avet-Loiseau et al. JCO 2010; 28: 4630-4*

Bortezomib as consolidation or maintenance treatment

Phase III: VTD vs TD as induction and consolidation (GIMEMA study)



Cavo et al. Blood 2010; 116(21); Abstract 42 (oral presentation)
Cavo et al. Lancet 2010; 376(9758): 2075-2085

Response data

Efficacy	VTD	TD	p
Induction			
≥nCR	31%	11%	<0.0001
After first ASCT			
≥nCR	52%	31%	<0.0001
After double ASCT			
≥nCR	55%	41%	0.002
After consolidation			
≥nCR	62%	45%	0.0002

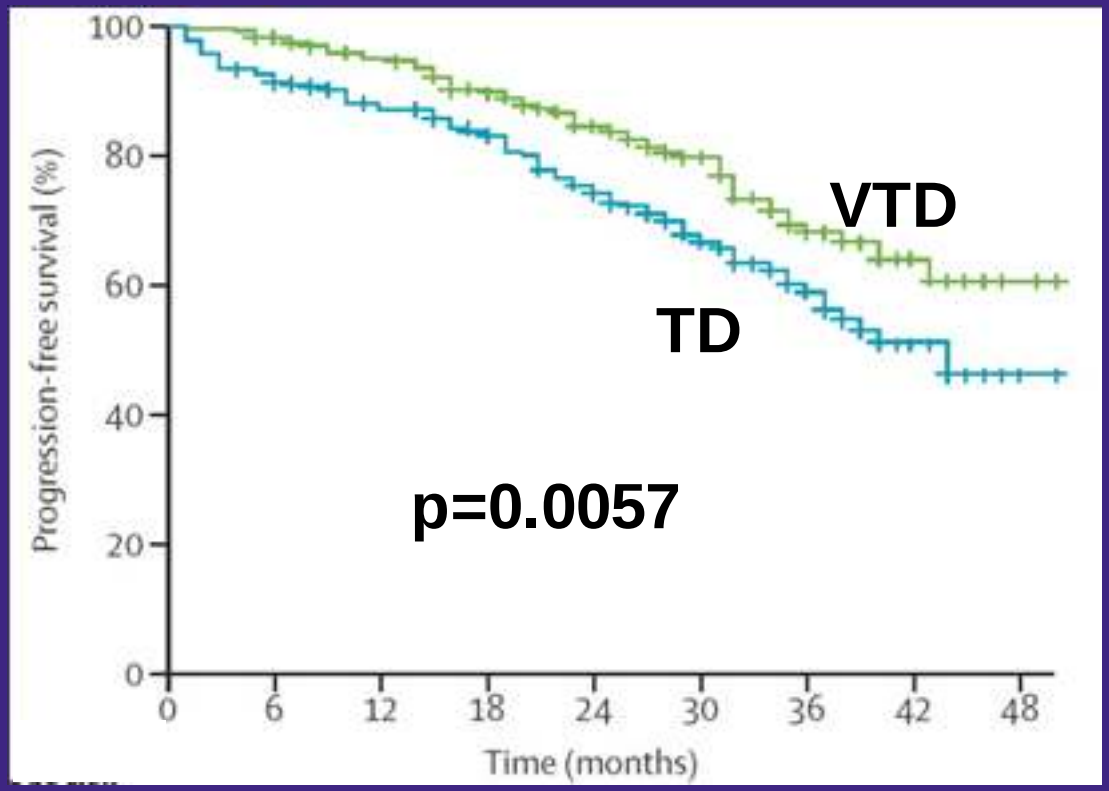
VTD consolidation increases rate of ≥nCR

Cavo et al. Blood 2010; 116(21); Abstract 42 (oral presentation)
Cavo et al. Lancet 2010; 376(9758): 2075-2085

Progression-free and overall survival

Median follow-up: 36 months

PFS



Estimated 3-year OS

- **VTD 86%**
- **TD 84%**

Significant PFS benefit with VTD compared to TD

Cavo et al. Blood 2010; 116(21); Abstract 42 (oral presentation)
Cavo et al. Lancet 2010; 376(9758): 2075-2085

Achieving molecular remission with VTD consolidation following transplant

- n=66 with ≥nCR after ASCT, treated with 2 cycles VTD or TD

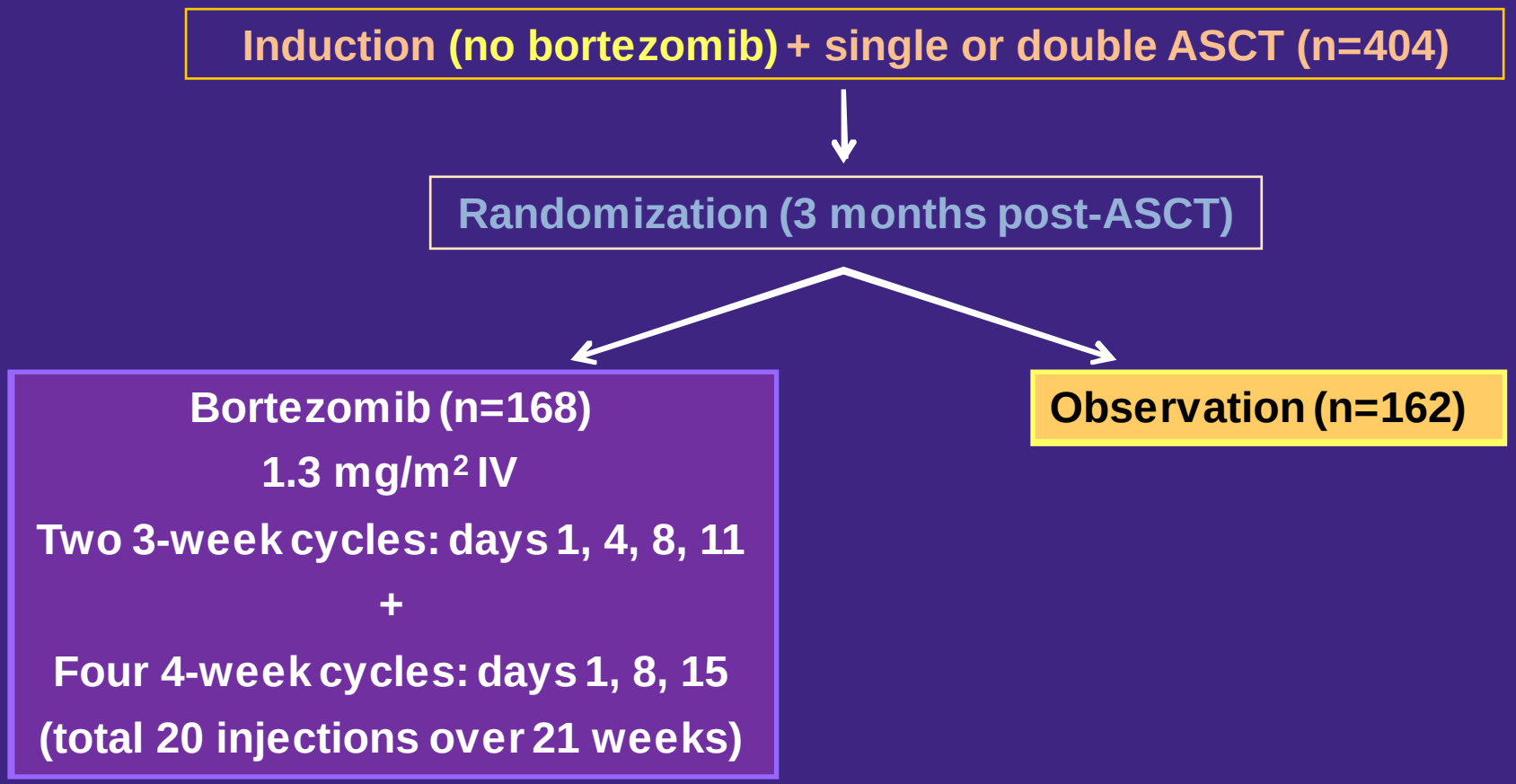
Efficacy (n=66)	VTD	TD	p
Pre-consolidation (day 0) PCR negativity	39%	31%	0.062
Post-consolidation (day +70) PCR negativity	64%	48%	0.007
Reduction in tumor burden post-consolidation (day +70) (real-time quantitative PCR)	Median 5 log reduction	Median 1 log reduction	0.05

VTD consolidation significantly reduced tumor burden compared to TD as detected by PCR

Terragna et al. Blood 2010; 116(21); Abstract 861 (oral presentation)

Phase III: bortezomib consolidation versus observation following ASCT

(Nordic Myeloma Study Group [NMSG 15/05] trial)



Updated study data to be presented by Dr. Mellqvist on Friday at 11:45 (Plenary Abstract Session II)

Mellqvist et al. Blood 2009; 114(22); Abstract 530 (oral presentation)

Phase III: bortezomib consolidation versus observation following ASCT (NMSG 15/05)

Preliminary results for 330 patients

	Bortezomib (n=168)	Observation (n=162)	p
Post-ASCT			
CR/nCR (%)	20	19	
Post-consolidation (6-months post-randomization)			
CR/nCR (%)	49	33	<0.01
Relapse during initial 6 months (%)	6	12	0.08

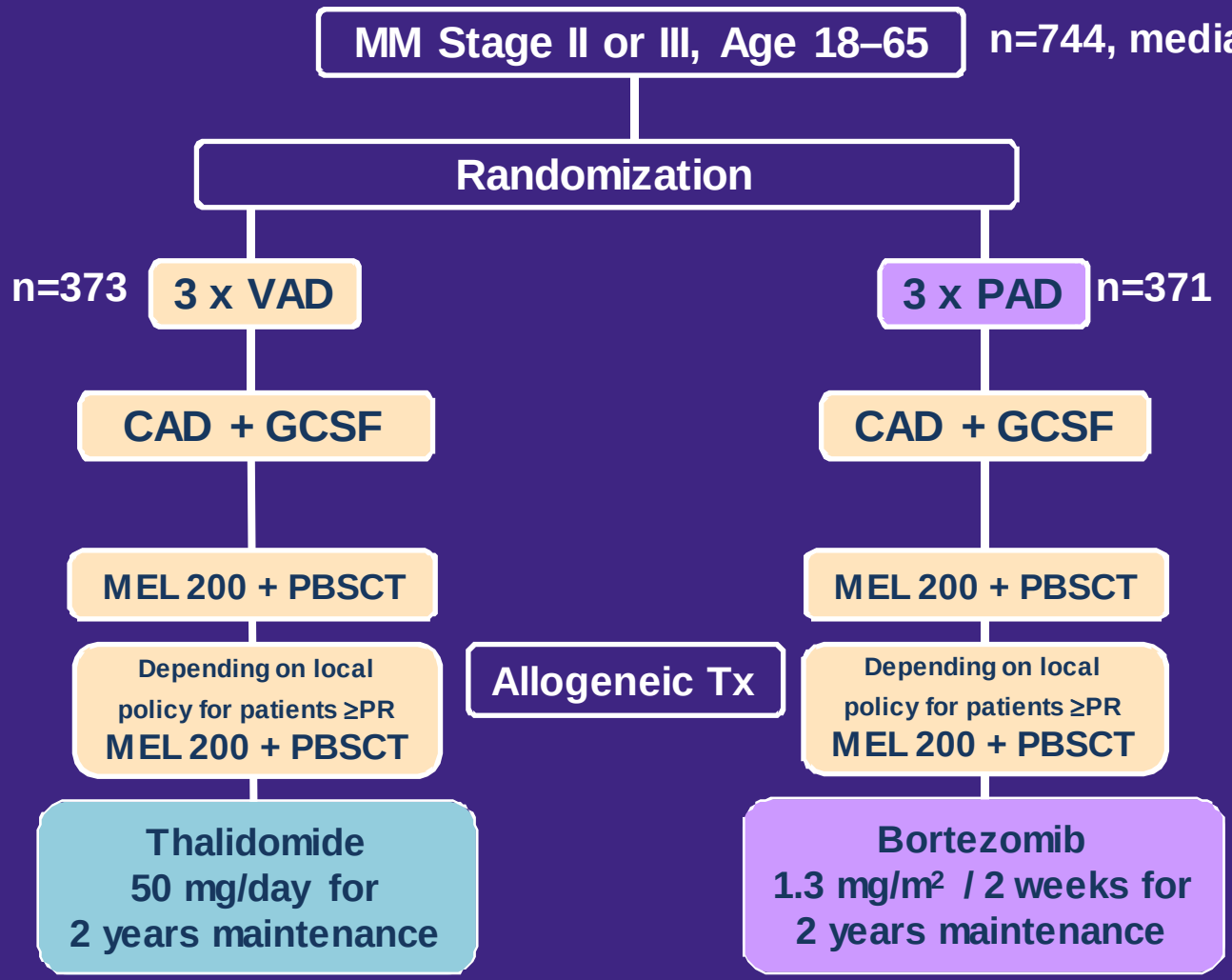
Consolidation with single agent bortezomib improves response after ASCT

Updated study data to be presented by Dr. Mellqvist on Friday at 11:45 (Plenary Abstract Session II)

Mellqvist et al. Blood 2009; 114(22); Abstract 530 (oral presentation)

Phase III: PAD vs VAD induction, HDM and bortezomib or thalidomide maintenance

HOVON 65 MM / GMMG-HD4 study



PAD:
Bortezomib 1.3 mg/m²
Doxorubicin 9 mg/m²
Dex 40 mg

Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)

Achievement of best response during maintenance therapy (%)

	Thalidomide arm	Bortezomib arm
Response after HDM (%)		
≥PR	77	88
≥VGPR	36	61
≥nCR	15	33
Improvement of response during maintenance		
<PR → PR	4	1
<VGPR → VGPR	13	11
<nCR → nCR	12	13
<CR → CR	10	12

Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)

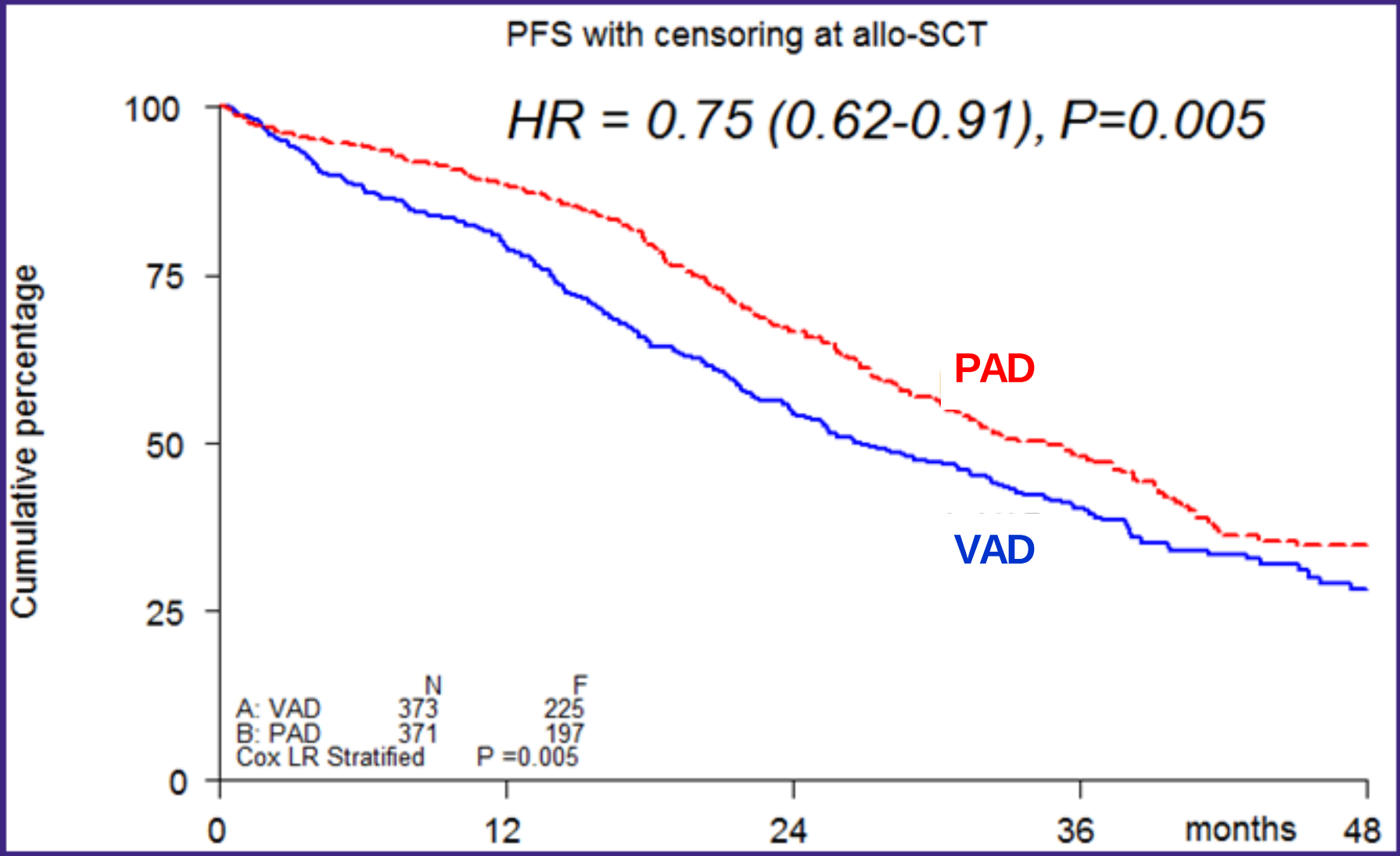
Adverse effects during 2 years of maintenance treatment

	VAD (%)		PAD (%)	
WHO CTC grade	2	3-4	2	3-4
Infections	35	18	40	24
GI	10	7	19	4
Neurotoxicity (PN)	26	15	14	9
Constitutional	24	2	14	2

Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)

Progression-free survival

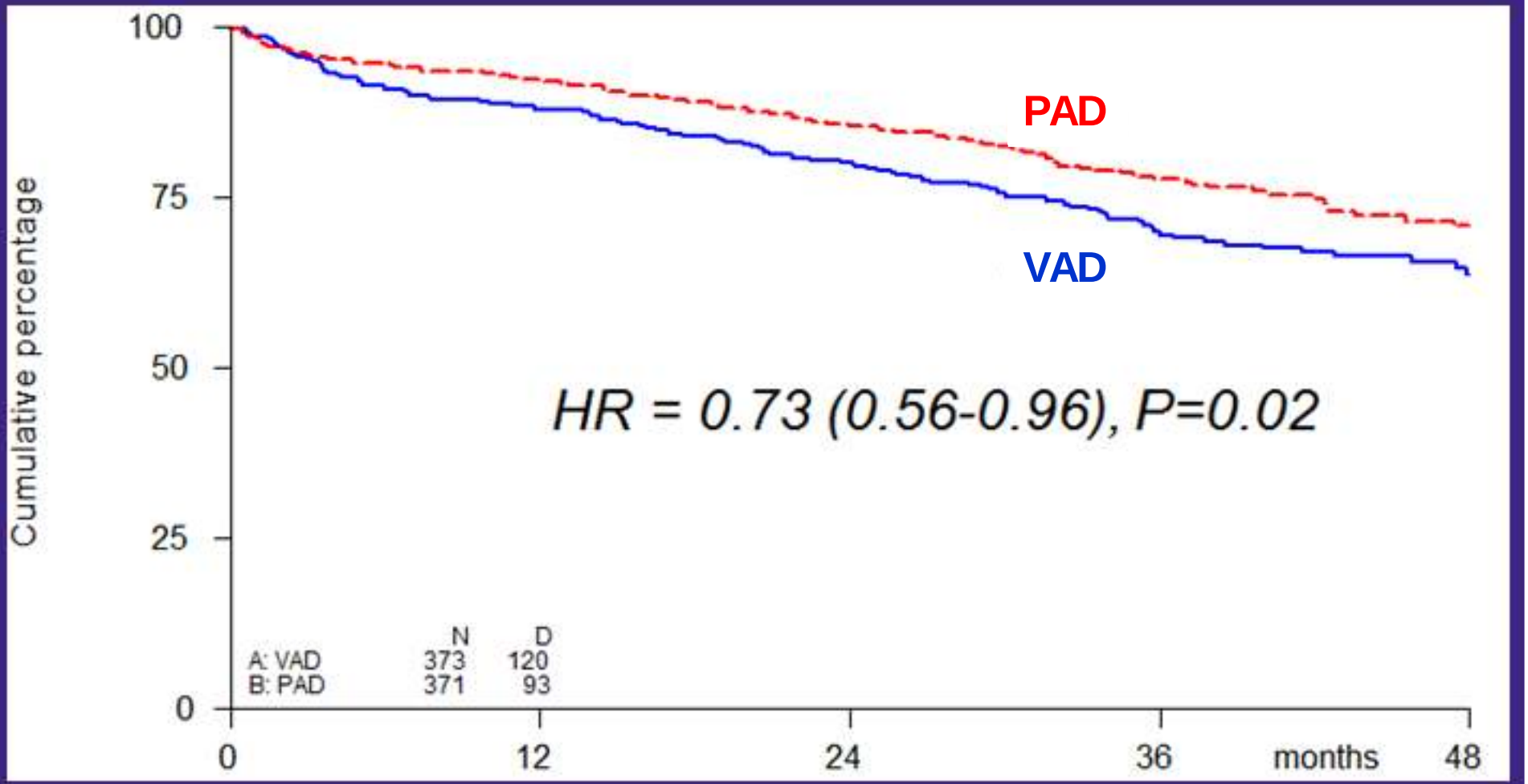
Median follow up: 39 months



Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)

Overall survival

Median follow up: 39 months



Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)

Summary: consolidation/maintenance

- **Bortezomib-containing regimens associated with significant**
  - **Increase in rates of CR/nCR and molecular remission[1-5]**
  - **Improvement in PFS (GIMEMA, HOVON/GMMG)[2,3,5]**
  - **Improvement in OS (HOVON/GMMG)[5]**

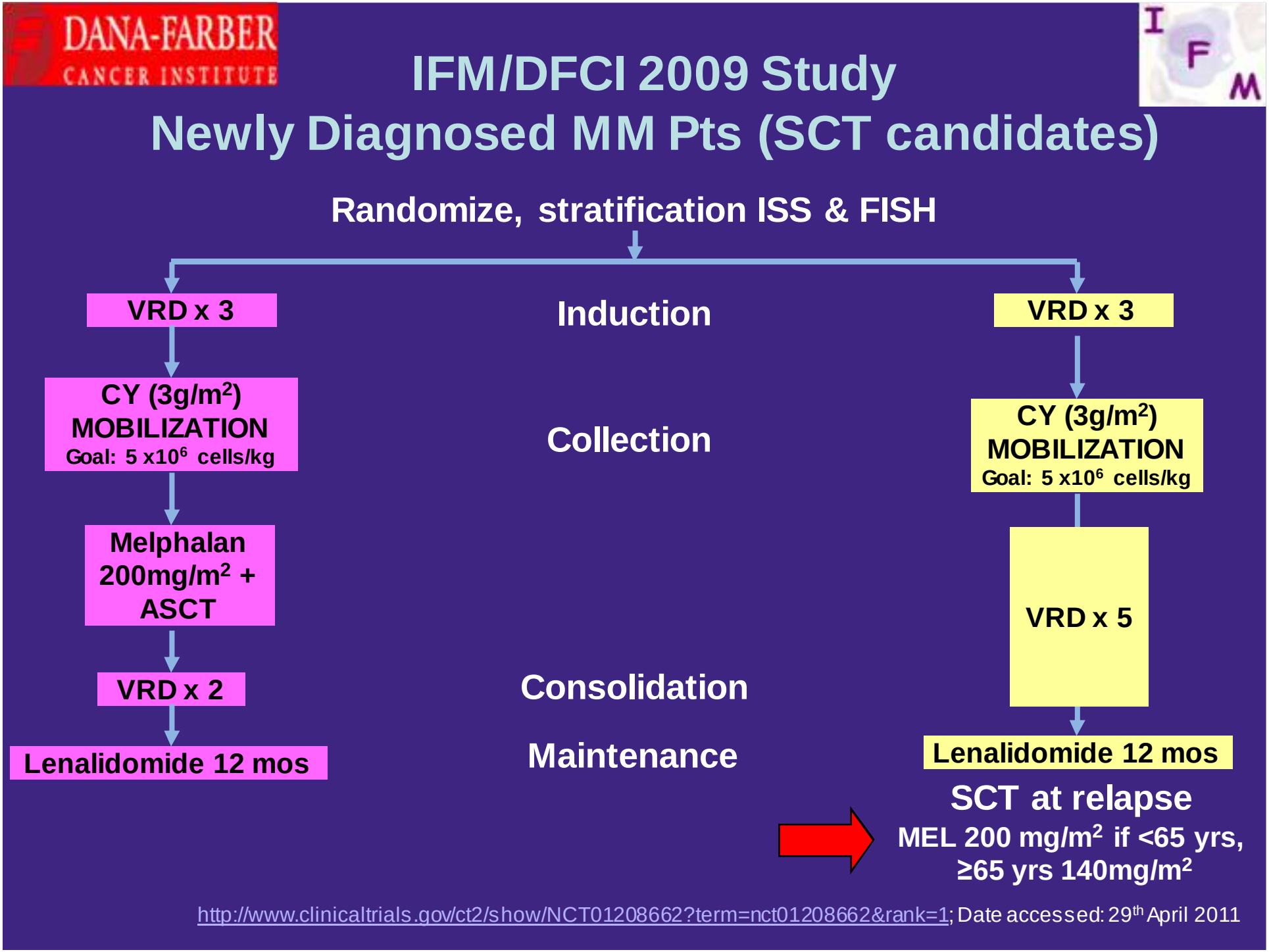
[1]*Mellqvist et al. Blood 2009; 114(22); Abstract 530 (oral presentation)*
[2]*Cavo et al. Blood 2010; 116(21); Abstract 42 (oral presentation)*
[3]*Cavo et al. Lancet 2010; 376(9758): 2075-2085*
[4]*Terragna et al. Blood 2010; 116(21); Abstract 861 (oral presentation)*
[5]*Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)*

Open questions

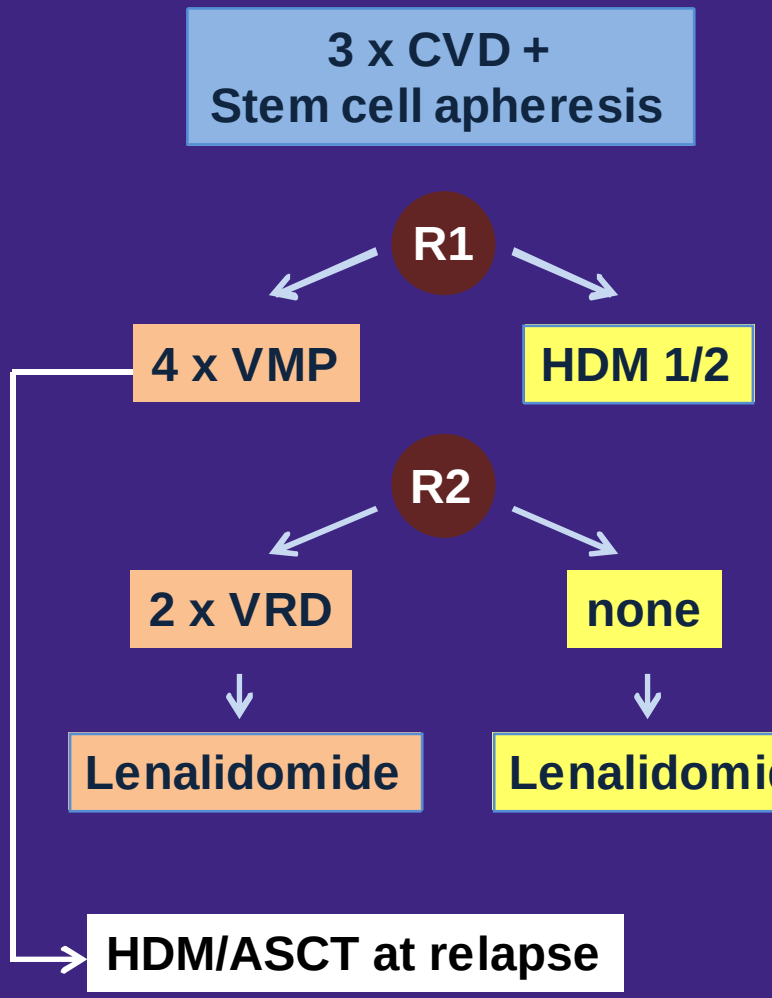
- **Do we still need transplant in the era of novel agents?**
- **Consolidation, maintenance or both?**
- **Molecular prognostic factors?**

What are our expectations?

- Tailored approach to therapy?
  - Identify groups of patients in whom early transplant is required versus patients in whom transplant could be delayed to relapse


DANA-FARBER CANCER INSTITUTE
IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)
Randomize, stratification ISS & FISH
VRD x 3
CY (3g/m2) MOBILIZATION
Goal: 5 x10^6 cells/kg
Melphalan 200mg/m2 + ASCT
VRD x 2
Lenalidomide 12 mos
Induction
Collection
Consolidation
Maintenance
VRD x 3
CY (3g/m2) MOBILIZATION
Goal: 5 x10^6 cells/kg
VRD x 5
Lenalidomide 12 mos
SCT at relapse
MEL 200 mg/m2 if <65 yrs,
≥65 yrs 140mg/m2
http://www.clinicaltrials.gov/ct2/show/NCT01208662?term=nct01208662&rank=1; Date accessed: 29th April 2011

Novel agents alone versus intensive therapy + novel agents: European Intergroup trial (EMN 02)



Induction

Stem cell mobilization in all patients

Consolidation

Maintenance

http://www.clinicaltrials.gov/ct2/show/NCT01208766?term=Sonneveld&rank=2; Date accessed: 29th April 2011

Summary and outlook

- **Novel agents have improved the outcome of high dose therapy followed by ASCT[1-6]**
- **Ongoing trials are examining the timing of transplantation in the era of novel agents[7,8]**

[1]*Harousseau et al. J Clin Oncol 2010; 28(30): 4621-4629*
[2]*Einsele et al. Blood 2009; 114(22); Abstract 131 (oral presentation)*
[3]*Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)*
[4]*Cavo et al. Lancet 2010; 376(9758): 2075-2085*
[5]*Rosinol et al. Blood 2010; 116(21); Abstract 307 (oral presentation)*
[6]*Moreau et al. J Clin Oncol 2010; 28(15 suppl): Abstract 8014 (oral presentation)*
[7]http://www.clinicaltrials.gov/ct2/show/NCT01208662?term=nct01208662&rank=1; Date accessed: 29th April 2011
[8]http://www.clinicaltrials.gov/ct2/show/NCT01208766?term=Sonneveld&rank=2; Date accessed: 29th April 2011


Optimizing Patient Outcomes Through Individualized Treatment Approaches: Phase III Data
Co-Chairs: Robert Orlowski, USA and
Pieter Sonneveld, The Netherlands
Med/MMa/FEB2011/EMEA045


Panel discussion
Moderated by Co-Chairs

Enhancing patient outcome through optimal management strategies: based on Phase III data

Med/MMa/FEB2011/EMEA045

Overcoming adverse effects through individualized patient care

Mohamad Mohty

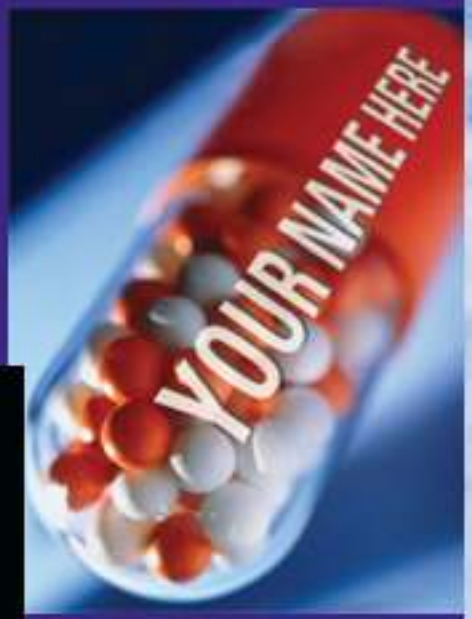
Med/MMa/FEB2011/EMEA045

Disclosures

Research Support/P.I.	Genzyme, Pierre-Fabre, Janssen, Celgene, Amgen, Roche, EUSA, Therakos
Employee	None
Consultant	Genzyme, Pierre-Fabre
Major Stockholder	None
Speakers Bureau	Genzyme, Pierre-Fabre, Janssen, Amgen, Gentium
Honoraria	Genzyme, Pierre-Fabre, Janssen, Celgene, Amgen, Roche, Therakos, Gentium
Scientific Advisory Board	SFGM-TC, EBMT

Presentation includes discussion of the off-label use of a drug or drugs

Individualized patient care: Hype or Reality?



Impact of novel agents in MM treatment

- **Significant contribution of novel agents to improved outcomes for patients[1]**
- **Extensive clinical experience[2,3]**
  - **"Learning-curve" regarding management of adverse events and comorbidities**
- **Better understanding of disease biology, individual disease characteristics[2,3]**
  - **Enabling tailored treatment / risk-adapted strategies**

[1]Kumar et al. Blood 2008; 111(5): 2516-2520
[2]Richardson. Blood 2010; 116(23): 4733-4734
[3]Palumbo and Anderson N Engl J Med 2011; 364(11): 1046-1060

Agenda

- **Focus on management of adverse events and comorbidities / complications**
  - **Thromboembolic complications**
  - **Peripheral neuropathy**
  - **Renal insufficiency**
  - **Bone disease**
  - ***Infectious complications, myelotoxicity etc.***

Multiple myeloma and thromboembolic complications

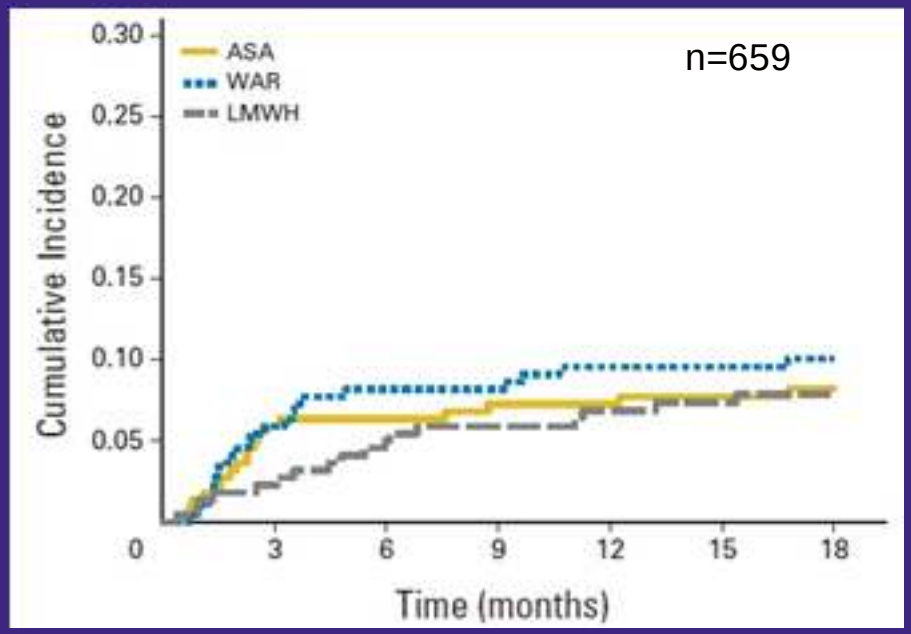
- **In MM, thromboembolic events have multifactorial causes[1]**
  - **Disease itself is thrombogenic**
  - **Hyperviscosity at diagnosis associated with higher risk**
  - **Some MM treatments are associated with VTEs**
  - **Supportive care with ESAs in combination with IMiDs ± chemotherapy has been noted to increase VTE rates[2]**
  - **Older age of patients associated with increased risk of VTEs**
  - **Classical non-specific risk factors: Immobilization, obesity, CVC or pacemaker, chronic cardiac or renal disease, multi-agent chemotherapy**

VTE, venous thrombolic event

[1]*Kristinsson. Hematology Am Soc Hematol Educ Program 2010; 2010: 437-444*
[2]*Knight et al. N Engl J Med 2006; 354(19): 2079-2080*

Thromboprophylaxis in MM

- **Randomization: n=667 receiving thal-containing regimens[1]**
  - **ASA (100 mg/d)**
  - **vs WAR (1.25 mg/d)**
  - **vs LMWH (enoxaparin 40 mg/d)**



- **Similar efficacy for ASA, WAR and LMWH in reducing serious TEs, acute CV events and sudden deaths**
- **In elderly pts: WAR showed less efficacy than LMWH**

[1]*Palumbo et al. J Clin Oncol 2011; 29(8): 986-993*

Risk-assessment model for the management of VTEs in MM patients treated with IMiDs

	Recommendation
Myeloma therapy High-dose dexamethasone Doxorubicin Multi-agent chemotherapy	LMWH or full-dose warfarin is recommended if thalidomide or lenalidomide is used in these combinations
Individual risk factors Obesity Previous VTE CVC or pacemaker Associated disease Cardiac disease Chronic renal disease Diabetes mellitus Acute infection Immobilization Surgery General surgery Any anesthesia Trauma Medication Erythropoietin Blood clotting disorders **Myeloma-related** Diagnosis Hyperviscosity	If no risk factor or any one risk factor is present: Aspirin 81–325 mg If two or more risk factors are present: LMWH or Full-dose warfarin (target INR 2-3)

Palumbo et al. Leukemia 2008; 22: 414-423 *Kristinsson SY. Hematology Am Soc Hematol Educ Program 2010; 2010: 437-444*

Incidence of DVT and PE with bortezomib

Phase III APEX[1]

	Bortezomib	Bortezomib + EPO
Patients (n)	194	137
DVT (%)	0	0.7
PE (%)	0	0.7

- No increased risk of TE events with bortezomib +/- dex and +/- EPO[1]

Phase III VISTA[2]

	VMP	VMP + ESA
Patients (n)	n=238	n=102
DVT (%)	1	2
PE (%)	1	1

- TE complications low and not affected by ESA use
- TTP and OS similar regardless of ESA use

DVT, deep vein thrombosis; PE, pulmonary embolism
TE, thromboembolic event

[1]*Lonial et al. Br J Haematol. 2008,143(2): 222-229*
[2]*Richardson et al. Br J Haematol. 2011 Mar 6 [Epub]*

Peripheral neuropathy (PN) in multiple myeloma

- Patients with MM are at risk of PN from
  - Disease
    - Baseline incidence
      - Newly diagnosed MM: <1–13%[1]
      - Relapsed/refractory MM (following multiple prior lines of therapy): 81% (with neurological examination)[2]
  - Treatment[3-5]
    - Conventional chemotherapy agents (e.g. vincristine), bortezomib, thalidomide, lenalidomide
  - Comorbid conditions[3-5]
    - Diabetes

[1]*Tariman et al. Clin J Oncol Nurs 2008; 12(3 Suppl): 29–36*
[2]*Richardson et al. J Clin Oncol 2006; 24(19): 3113–3120*
[3]*Delforge et al. Lancet Oncol 2010; 11(11):1086-1095*
[4]*Mohty et al. Haematologica 2010; 95(2): 311-319*
[5]*Sonneveld et al. Hematology Am Soc Hematol Educ Program 2010; 2010: 423-430*

Thalidomide-induced PN

- **Closely related to dose and treatment duration (main risk factors for development of PN)**

- **Mainly sensory neuropathy**
  - **Numbness, tingling, pinprick sensation, sensitivity in toes and fingers are the most common symptoms**
  - **Painful neuropathy may occur with chronic use**
  - **Absence of reflexes and loss of proprioception may occur**
- **Motor symptoms rarely seen**
- **Autonomic symptoms**
  - **Dizzy spells, bradycardia, sexual dysfunction, constipation**

Delforge et al. Lancet Oncol 2010; 11(11): 1086-1095
Mohty et al. Haematologica 2010; 95(2): 311-319
Sonneveld et al. Hematology Am Soc Hematol Educ Program 2010; 2010: 423-430

Bortezomib-induced PN

- Occurs after median 2–3 months, maximum around cycle 5, followed by plateau (role of cumulative dose effect unknown?)[1-3]
- Not all patients will develop PN (genetic factors?)
- Prior history of PN is a significant risk factor[3]
- Mainly sensory neuropathy
  - Numbness, tingling, pinprick sensation, sensitivity in toes and fingers are the most common symptoms
  - Painful neuropathy
    - Sharp or burning; associated with altered heat and cold sensation
    - Localized in toes, soles of feet, sometimes fingertips and palms
- Motor symptoms rare
- Autonomic symptoms: orthostatic hypotension, GI side effects

[1]*Delforge et al. Lancet Oncol 2010; 11(11): 1086-1095*
[2]*Mohty et al. Haematologica 2010; 95(2): 311-319*
[3]*Sonneveld et al. Hematology Am Soc Hematol Educ Program 2010; 2010: 423-430*

Managing peripheral neuropathy

- **Close monitoring of patients**
  - Regular assessments
    - Prior to each administration and during therapy
    - Neurophysiologic testing recommended in specific situations
  - Multidisciplinary approach involving patients, nurses, hemato-oncologists, neurologists

  - **Need to actively ask about symptoms with specific questions**
    - Patients rarely complain!
    - In case of doubtful assessment: go for the higher grade!

- **Prompt action crucial**
  - Dose reduction, schedule modification
  - Switch to non-neurotoxic agent
  - Symptom relief

Delforge et al. Lancet Oncol 2010; 11(11):1086-1095
Mohty et al. Haematologica 2010; 95(2): 311-319
Sonneveld et al. Hematology Am Soc Hematol Educ Program 2010; 2010: 423-430

Managing peripheral neuropathy

Monitoring patients using a dedicated assessment tool:

- **Questionnaire helps to increase awareness of symptoms and provides a framework for tracking changes**

Selected questions

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my hands/feet					
I get a ringing or buzzing in my ears					
I have trouble buttoning buttons					
I have trouble feeling the shape of small objects when they are in my hands					
I have trouble walking					

Close monitoring and prompt action prevent / reduce neurotoxicity significantly

Colson et al. Cancer Nurs 2008; 31: 239-249

Dose modifications for thalidomide-induced neurotoxicity

Recommended dose modifications for Thalidomide (Celgene) related neuropathy in first line treatment of MM (Summary of Product Characteristics)

Severity of PN signs and symptoms*	Modification of dose and regimen
Grade 1 (paresthesia, weakness and/or loss of reflexes) with no loss of function	Continue to monitor the patient with clinical examination. Consider reducing dose if symptoms worsen. However, dose reduction not necessarily followed by improvement of symptoms.
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose or interrupt treatment and continue to monitor patient with clinical and neurological examination. If no improvement or continued worsening of neuropathy, discontinue treatment. If neuropathy resolves to Grade 1 or better, treatment may be restarted, if benefit/risk is favorable.
Grade 3 (interfering with activities of daily living)	Discontinue treatment
Grade 4 (neuropathy which is disabling)	Discontinue treatment

Thalidomide Summary of Product Characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000823/WC500037050.pdf; Accessed 3 May 2011

Expert recommendations: Dose modifications for thalidomide-induced neurotoxicity

Grade 1	**Reduce thalidomide dose by 50%**
Grade 2	**Discontinue thalidomide** **If neuropathy resolves to grade 1 or better, treatment may be restarted at 50% dose reduction**
Grade 3	**Discontinue thalidomide**
Grade 4	**Discontinue thalidomide**

If sensory PN is associated with neuropathic pain, CTC score is upgraded one severity level

Delforge et al. Lancet Oncol 2010; 11(11): 1086-1095
Mohty et al. Haematologica 2010; 95(2): 311-319
Sonneveld et al. Hematology Am Soc Hematol Educ Program 2010; 2010: 423-430

Dose modifications for bortezomib-induced neurotoxicity (Summary of Product Characteristics)

Severity of PN signs and symptoms*	Modification of dose and regimen
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce bortezomib to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib therapy until toxicity resolves, When toxicity resolves, reinitiate bortezomib at a reduced dose of 0.7 mg/m^2 Change treatment schedule to once per week
Grade 4 (Sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue bortezomib

*National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0, Dec. 2003

VELCADE Summary of Product Characteristics; 17 January 2011

Expert recommendations: Dose modifications for bortezomib-induced neurotoxicity

Grade 1	If patient is on twice-weekly schedule[†]: reduce current bortezomib dose by one level[‡] or prolong dosing interval to once-weekly If patient is on once-weekly schedule: reduce bortezomib dose by one level[‡]
Grade 2	If patient is on twice-weekly schedule: reduce bortezomib dose by on level[‡] or prolong dosing interval to once-weekly If patient is on once-weekly schedule: reduce bortezomib dose by one level[‡] or consider temporary discontinuation If neuropathy resolves to grade 1 or better, once-weekly bortezomib at reduced dose may be restarted
Grade 3	Discontinue bortezomib
Grade 4	Discontinue bortezomib

[†]Patients ≥75 years may be immediately started on once-weekly regimen when initiating bortezomib
[‡]Bortezomib dose reductions: standard dose: 1.3 mg/m^2; dose reduced by 1 level: 1.0 mg/m^2; dose reduced by 2 levels: 0.7 mg/m^2
If sensory PN is associated with neuropathic pain, CTC score is upgraded one severity level.

Delforge et al. Lancet Oncol 2010; 11(11): 1086-1095
Mohty et al. Haematologica 2010; 95(2): 311-319
Sonneveld et al. Hematology Am Soc Hematol Educ Program 2010; 2010: 423-430

Bortezomib dose modification is an efficient strategy to improve/resolve PN

Phase II: SUMMIT & CREST[1]

- Patients ≥Grade 3 PN:
  - Resolution or improvement in 71%

Phase III: APEX[2]

- Patients ≥Grade 2 PN:
  - Resolution or improvement in 64%

Phase III: VISTA[3]

- Patients ≥Grade 2 PN:
  - Resolution in 60%
  - Improvement in 79%

In clinical trials, bortezomib-associated PN was reversible in most cases following dose reduction or discontinuation

[1]*Richardson et al. J Clin Oncol 2006; 24: 3113-3120*
[2]*Richardson et al. Br J Haematol 2009; 144(6): 895-903*
[3]*Mateos et al. J Clin Oncol 2010; 28: 2259-2266*

Therapeutic interventions for PN

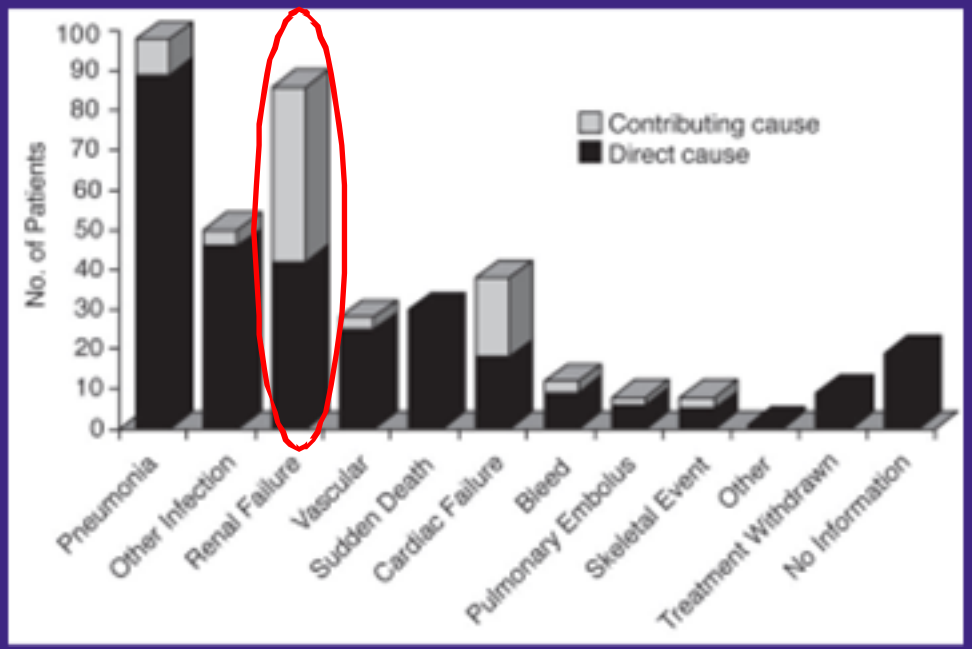
- **Pharmacologic interventions**
  - Pregabalin, Gabapentin
  - Amitriptyline, duloxetine
  - Topical lidocaine, capsaicin cream
  - Tramadol, morphine, oxycodone
- **Vitamins and supplements**
  - Multi-B complex vitamins (B1, B6, B12), fish oils, magnesium, potassium, folic acid, acetyl-L-carnitine, α-lipoic acid, glutamine, tonic water
- **Emollient creams**
  - Cocoa butter, menthol- and eucalyptus-based creams
- **Therapeutic massage**

Colvin et al. J Clin Oncol 2008; 26(27): 4519-4520
Mohty et al. Haematologica 2010; 95(2): 311-319
Richardson et al. JNCCN 2010; 8[Suppl 1]: S4–S12
Sonneveld et al. Hematology Am Soc Hematol Educ Program 2010; 2010: 423-430
Delforge et al. Lancet Oncol 2010; 11(11): 1086-1095

Renal impairment/failure in multiple myeloma

- **Incidence**
  - Renal impairment in newly diagnosed patients: 20–40%[1–3]
  - Renal failure: 20%[2]
- **Impact**
  - Associated with increased probability of early death and susceptibility to infections[2,4]

Early mortality before day 60 in MRC trials 1980-2002 (n=3,107)[4]



Renal failure was contributory to 86 early deaths (28%)

[1]*Alexanian et al. Arch Intern Med 1990;150: 1693-1695*
[2]*Blade et al. Arch Intern Med 1998;158: 1889-1893*
[3]*Kyle et al. Mayo Clin Proc 2003;78: 21-33*
[4]*Augustson et al. J Clin Oncol 2005;23: 9219-9226*

Renal impairment/failure in multiple myeloma

- **Causes**[1,2]
  - **Accumulation of monoclonal light chains: cast nephropathy**
  - **Dehydration**
  - **Hypercalcemia**
  - **Use of nephrotoxic drugs**
- **Medical emergency requiring prompt intervention**[1,3]
  - **Reduction in myeloma burden to reduce light chain load**
  - **Supportive care**
- **Prompt initiation of treatment is a critical determinant of renal recovery**[3]

[1]*Dimopoulos et al. Leukemia 2008; 22: 1485-1493*
[2]*Dimopoulos et al. Hematology Am Soc Hematol Educ Program 2010; 431-436*
[3]*Cockwell et al. Curr Opin Nephrol Hypertens 2010; 19: 550-555*

Rationale for use of bortezomib in patients with myeloma-induced renal impairment

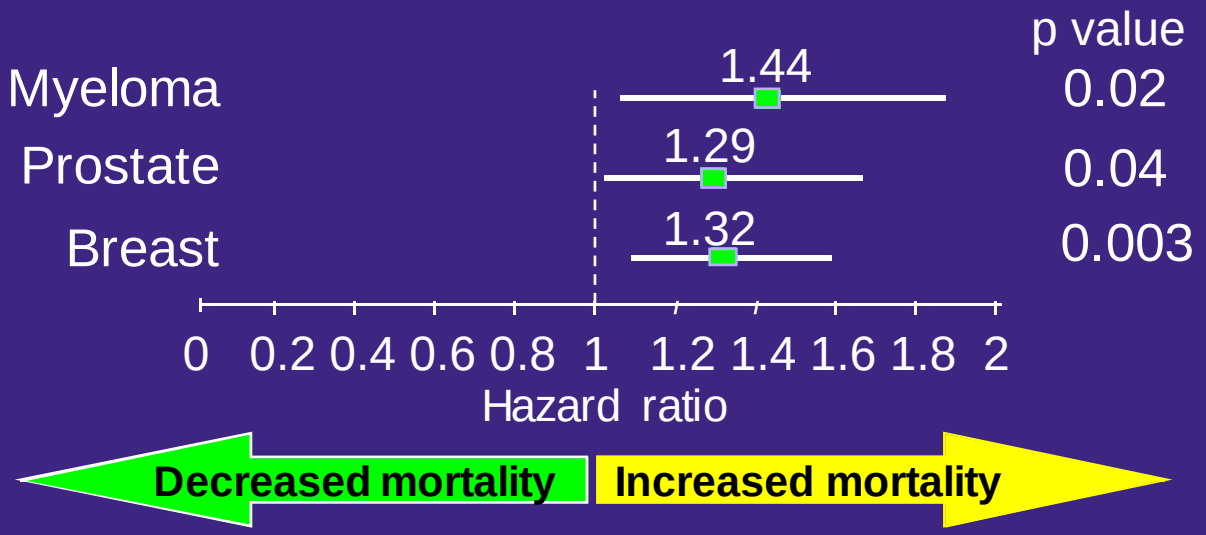
- **Short time to response[1]**
- **High overall and complete responses in combination regimens[2-6]**
- **Well tolerated: toxicity similar in patients with and without renal impairment[1,7]**
- **Bortezomib clearance independent of renal function[8]**
- **Reduces inflammation in myeloma kidney disease[9,10]**
- **Reversal of renal failure in approximately 2/3 of patients across studies[7,11-14]**

[1]San Miguel et al. Leukemia 2008; 22: 842-849
[2]San Miguel et al. N Engl J Med 2008; 359: 906-917
[3]Kropff et al. Br J Haematol 2007; 138: 330-337
[4]Popat et al. Br J Haem 2009; 144: 887-894
[5]Reece et al. J Clin Oncol 2008; 26: 4777-4783
[6]Orlowski et al. J Clin Oncol 2007; 25(25): 3892-3901
[7]Dimopoulos et al. J Clin Oncol 2009; 27: 6086-6093
[8]Mulkerin et al. Blood 2007; 110: (Abstract 3477)
[9]Mezzano et al. Kidney Int 2001; 60(4): 1366-1377
[10]Ludwig et al. Haematologica 2007; 92: 1411-1414
[11]Kastritis Haematologica 2007; 92: 546-549
[12]Roussou Leuk Lymphoma 2008; 49: 890-895
[13]Ludwig JCO 2010; 28: 4635-4641
[14]Roussou Leukemia Res 2010; 34: 1395-1397

Bone disease in multiple myeloma

- **Associated with significant morbidity and reduced QoL due to skeletal complications**

- **High incidence of bone involvement present in up to 90% of patients:**
  - **Imbalance between bone formation and bone destruction (suppression of osteoblast function and enhancement of osteoclast activity)**



Saad F, et al. Cancer. 2007; 110(8): 1860-1867

Terpos et al. Blood 2007; 110(4): 1098-1104
Terpos et al. Ann Oncol 2009; 20: 1303-1317

Treatment of MM bone disease

- Analgesia
- Bisphosphonates
- Surgical procedures
  - Vertebroplasty
  - Kyphoplasty
- Radiotherapy
- Specific disease treatment
- Investigational agents targeting specific factors involved in bone resorption/formation

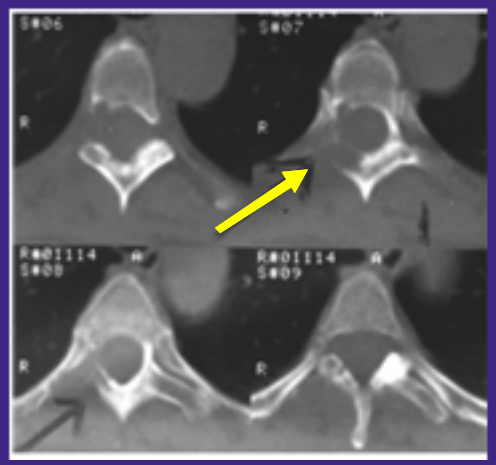
Terpos et al. Ann Oncol 2009;20: 1303-17

Bortezomib: Effect on bone remodelling

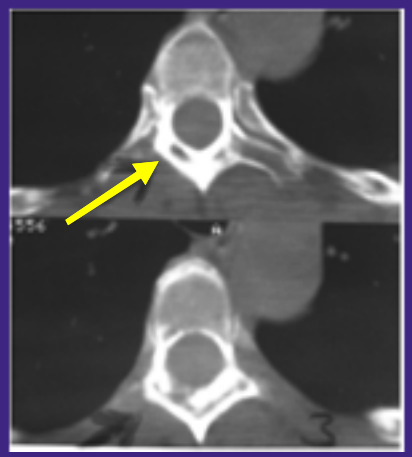
- **Preclinical and clinical studies: Bortezomib increases osteoblast activity and inhibits osteoclast activity[1-3]**
- **Beneficial impact (bone healing) observed in patients with MM and advanced osteolytic disease treated with bortezomib[4-7]**

CT scans of lytic lesions in thoracic vertebra in patient with CR to VMP[7]

Baseline



Cycle 9



[1]*Giuliani et al. Blood 2007; 110: 334-8*
[2]*Pennisi et al. Am J Hematol 2009; 84: 6-14*
[3]*Terpos et al. Blood 2007; 110(4): 1098-104*
[4]*Lund et al. Eur J Haematol 2010; 85(4): 290-299*
[5]*Zangari et al. Haematologica 2011; 96(2): 333-336*
[6]*Terpos et al. Ann Oncol 2010; 21(7): 1561-1562*
[7]*Delforge et al. Eur J Haematol 2011 Mar 2 [Epub]*

Summary

- **Improvement in side effects management through clinical experience:**
  - **Thrombo-prophylaxis based on risk factors[1]**
  - **Effective PN management: close monitoring and prompt action[2-4]**
- **Renal insufficiency:**
  - **Requires prompt intervention with effective anti-myeloma agents and supportive care[5]**
  - **Reversal of renal failure in substantial proportion of patients with bortezomib treatment[5]**
- **MM bone disease:**
  - **Bisphosphonates remain the mainstay of treatment[6]**
  - **Increased bone formation seen with bortezomib[7]**

[1]*Palumbo et al. Leukemia 2008; 22: 414-423*
[2]*Delforge et al. Lancet Oncol 2010; 11(11): 1086-1095*
[3]*Mohty et al. Haematologica 2010; 95(2): 311-319*
[4]*Sonneveld et al. Hematology Am Soc Hematol Educ Program 2010; 423-430*
[5]*Dimopoulos et al. J Clin Oncol 2010; 28: 4976-4984*
[6]*Terpos et al. Ann Oncol 2009; 20: 1303-1317*
[7]*Delforge et al. Eur J Haematol 2011 Mar 2 [Epub]*

Multiple Myeloma Tailored Therapy !

28 May 2001

"I Never Think of the Future –
It Comes Soon Enough."
A. Einstein (1879-1955)


Optimizing Patient Outcomes Through Individualized Treatment Approaches: Phase III Data
Co-Chairs: Robert Orlowski, USA and
Pieter Sonneveld, The Netherlands
Med/MMa/FEB2011/EMEA045


Practical considerations for patient management
Kathleen Colson
Med/MMa/FEB2011/EMEA045

Disclosures

Research Support/P.I.	None
Employee	None
Consultant	Millennium
Major Stockholder	None
Speakers Bureau	None
Honoraria	Millennium
Scientific Advisory Board	None

Presentation includes discussion of the off-label use of a drug or drugs

Impact of myeloma diagnosis

- **Profound effect on patients, family, caregivers**
- **Emotional impact**
  - **Shock, disbelief, powerlessness, fear, anxiety, guilt, sadness, grief, depression, anger**
- **Sense of isolation and confinement**
- **Significant impact on psychological health and QoL**
- **Financial issues**

Kelly M. Oncology News 2007;1: 20-21
Molassiotis et al. Psychooncology 2011;20(1):88-97

Importance of information and support

- **Why is information important?**
  - **Sense of control**
  - **Assists decision-making**

- **Where to get information and support?**
  - **Nurses, physicians**
  - **Patient organizations, support groups**
  - **Internet**

http://www.myeloma.org.uk/
http://www.myeloma-euronet.org/
http://myeloma.org/

Patient expectations

- Suitable and adequate information
  - Opportunity to ask questions
- Realistic discussion on prognosis, treatment options
- Involvement in treatment decisions
- Information about clinical trials / new treatments

http://www.myeloma.org.uk/
http://www.myeloma-euronet.org/
http://myeloma.org/

Key role for hematology nurses in coordinating care

- **Direct care provision**
  - Knowledge of disease, treatments, potential complications
  - Promote physical and psychological well-being, overall QoL
- **Monitoring**
  - Regular contact enables
    - early detection of side effects, initiation of interventions
    - checking of adherence to treatments

Kelly M. Oncology News 2007; 1: 20-21

Key role for hematology nurses in coordinating care

- **Patient education**
  - Flood of information following diagnosis overwhelming
  - Information on treatment choices, toxicities, measures to minimise risks of complications
- **Communication and patient advocate**
  - Continuity in patient care; often main point of contact in hospital
  - Ensuring care is patient-focussed and individualized

Kelly M. Oncology News 2007; 1: 20-21

Importance of nurse-specific recommendations for side effect management

Consensus statements by IMF Nurse Leadership Board

- Nurse Leadership Board (NLB) created by IMF
  - Oncology nurses from cancer centers and community practices
- NLB management recommendations for key AEs of novel agents
  - Myelosuppression, thromboembolic events, peripheral neuropathy, steroid toxicities, gastrointestinal side effects

IMF: International Myeloma Foundation

Bertolotti P et al. Clin J Oncol Nurs 2008; 12(3 Suppl): 9-12
Miceli T et al. Clin J Oncol Nurs 2008; 12(3 Suppl): 13-20
Rome S et al. Clin J Oncol Nurs 2008; 12(3 Suppl): 21-28
Smith LC et al. Clin J Oncol Nurs 2008; 12(3 Suppl): 37-52
Faiman B et al. Clin J Oncol Nurs 2008; 12(3 Suppl): 53-63

Nursing considerations regarding specific side effects

Side effects and nursing considerations

Side effect	Possible intervention
Diarrhea	• Fluid intake • Fiber supplements • Antidiarrheals • Referral to nutritionist
Constipation	• Dietary considerations • Stool softeners, laxatives • Referral to nutritionist
Nausea and vomiting	Anti-emetics
Anorexia	Appetite stimulants

Colson et al. Cancer Nurs 2008; 31(3): 239-249

Side effects and nursing considerations

Side effect	Possible intervention
Asthenia and fatigue	• Rest, nutrition, hydration, exercise • Antidepressants, psychiatric referral
Thrombocytopenia	• Monitor blood counts • Platelet transfusion
Neutropenia and anemia	• Monitor blood counts • Transfusions and hematopoietic growth factors

Colson et al. Cancer Nurs 2008; 31(3): 239-249

Side effects and nursing considerations

Side effect	Possible intervention
Peripheral neuropathy	• Thorough baseline assessment • Regular monitoring
Hypotension	• Monitor concomitant medications • Monitor blood pressure
Electrolyte imbalances	• Monitor blood chemistries • Magnesium, potassium supplements • Dietary considerations • Fluid intake
Rash and pyrexia	• Diphenhydramine and cortisone creams, acetaminophen (paracetamol) • Low-dose oral corticosteroids

Colson et al. Cancer Nurs 2008; 31(3): 239-249

Survivorship Care Plan

- **Aims**
  - Summarize treatment; communicate late effects of treatment
  - Promote continuous communication between patients and healthcare providers
  - Promote healthy lifestyle

- **Clinical nurse-specific practice-based consensus documents**
  - Topics
    - Renal complications
    - Sexuality and sexual dysfunction
    - Bone disease and bone health
    - Functional mobility and safety
    - Health maintenance
  - Publication: 2nd quarter 2011

Summary

- **Profound effect of myeloma diagnosis on patients, family[1,2]**
  - **Importance of information and support**
- **Key role for hematology nurses in coordinating and providing care[1]**
  - **Supportive treatments**
  - **Communication and education**
- **Nurse-specific recommendations developed to improve patient management[3-7]**

[1]*Kelly M. Oncology News 2007;1:20-21*
[2]*Molassiotis et al. Psychooncology 2011; 20(1): 88-97*
[3]*Bertolotti P et al. Clin J Oncol Nurs 2008;12(3 Suppl):9-12*
[4]*Miceli T et al. Clin J Oncol Nurs 2008;12(3 Suppl):13-20*
[5]*Rome S et al. Clin J Oncol Nurs 2008;12(3 Suppl):21-28*
[6]*Smith LC et al. Clin J Oncol Nurs 2008;12(3 Suppl):37-52*
[7]*Faiman B et al. Clin J Oncol Nurs 2008;12(3 Suppl):53-63*


Optimizing Patient Outcomes Through Individualized Treatment Approaches: Phase III Data
Co-Chairs: Robert Orlowski, USA and
Pieter Sonneveld, The Netherlands
Med/MMa/FEB2011/EMEA045

Flexible dosing strategies and subcutaneous route of administration: Phase III data

Michel Delforge

Med/MMa/FEB2011/EMEA045

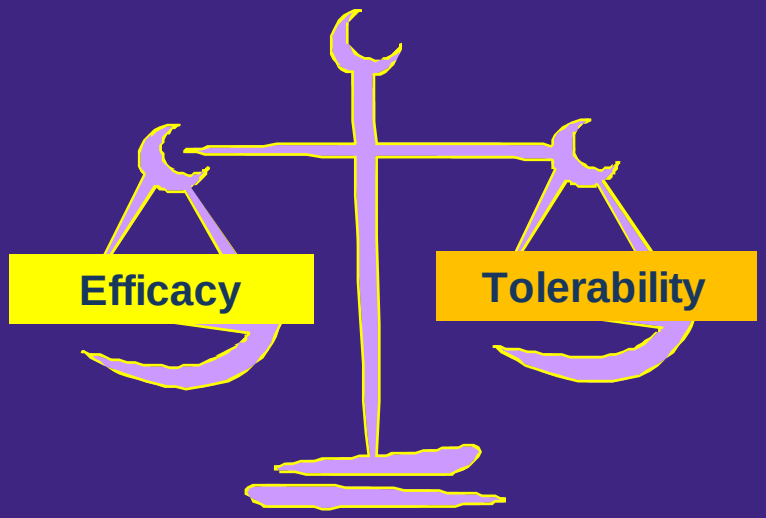
Disclosures

Research Support/P.I.	None
Employee	None
Consultant	Janssen, Celgene
Major Stockholder	None
Speakers Bureau	Janssen, Celgene
Honoraria	Janssen, Celgene, Novartis
Scientific Advisory Board	None

Presentation includes discussion of the off-label use of a drug or drugs

Treatment considerations

- Aim: deliver effective treatment while maintaining quality of life



- Important for all patients, especially vulnerable patients
- How to optimize bortezomib administration?
  - Once-weekly dosing
  - Subcutaneous vs intravenous

Flexible dosing with bortezomib

- **Two large phase III trials investigated once-weekly administration of bortezomib**
  - **VMP vs VTP followed by VT or VP maintenance in newly diagnosed elderly patients with MM (PETHEMA/GEM)[1]**
  - **VMPT plus VT maintenance vs VMP in elderly patients (GIMEMA)[2,3]**

[1]*Mateos et al. Lancet Oncol 2010; 11: 934-941*
[2]*Palumbo et al. J Clin Oncol 2010; 28: 5101-5109*
[3]*Bringhen et al. Blood 2010; 116: 4745-4753*

Overview of VMP schedules in phase III trials

Study	Treatment duration	Dosing
VISTA: VMP[1-3] N=682	**4 twice-weekly 6-week cycles** **+** **5 once-weekly 6-week cycles**	**Bortezomib 1.3 mg/m^2** **Melphalan 9 mg/m^2** **Prednisone 60 mg/m^2**
Modified VISTA schedules: once weekly bortezomib		
GIMEMA: VMP[4,5] N=511	**9 once-weekly 5-week cycles**	**Bortezomib 1.3 mg/m^2** **Melphalan 9 mg/m^2** **Prednisone 60 mg/m^2**
PETHEMA/GEM: VMP[6] N=260	**1 twice-weekly 6-week cycle** **+** **5 once-weekly 5-week cycles**	**Bortezomib 1.3 mg/m^2** **Melphalan 9 mg/m^2** **Prednisone 60 mg/m^2**

[1]*San Miguel et al. NEJM 2008; 359: 906-917*
[2]*San Miguel et al. NEJM 2008; 359: 906; Suppl. App.*
[3]*Mateos et al. J Clin Oncol 2010; 28: 2259-2266*
[4]*Palumbo et al. J Clin Oncol 2010; 28: 5101-5109*
[5]*Bringhen et al. Blood 2010; 116: 4745-4753*
[6]*Mateos et al. Lancet Oncol 2010; 11: 934-941*

Once-weekly vs twice-weekly bortezomib: Comparable efficacy with improved tolerability

Study details	Efficacy				Sensory PN		Discont. due to PN	Discont. due to AEs overall
	ORR	CR	Median PFS	3-year OS	All grades	Grade 3/4		
Twice-weekly VMP								
VISTA[1-3]	71%	30%	21.7m	68.5%	44%	13%	15%	34%
Once-weekly VMP								
GIMEMA[4,5]	79%	23%	27m	87%	22%	2%	4%	17%
PETHEMA/GEM[6]	80%	20%	34m	74%	NR	7%	NR	12%†

NR: not reported

†Discontinuations due to SAEs

[1]San Miguel et al. NEJM 2008; 359: 906-917
[2]San Miguel et al. NEJM 2008; 359: 906; Suppl. App.
[3]Mateos et al. J Clin Oncol 2010; 28: 2259-2266
[4]Palumbo et al. J Clin Oncol 2010; 28: 5101-5109
[5]Bringhen et al. Blood 2010; 116: 4745-4753
[6]Mateos et al. Lancet Oncol 2010; 11: 934-941

Expert recommendations: Dose modifications for bortezomib-induced neurotoxicity

Summary of product characteristics guidelines modified according to expert opinion and clinical practice in reference centres:

Grade 1	If patient is on twice-weekly schedule[†]: reduce current bortezomib dose by one level[‡] or prolong dosing interval to once-weekly If patient is on once-weekly schedule: reduce bortezomib dose by one level[‡]
Grade 2	If patient is on twice-weekly schedule: reduce bortezomib dose by on level[‡] or prolong dosing interval to once-weekly If patient is on once-weekly schedule: reduce bortezomib dose by one level[‡] or consider temporary discontinuation If neuropathy resolves to grade 1 or better, once-weekly bortezomib at reduced dose may be restarted
Grade 3	Discontinue bortezomib
Grade 4	Discontinue bortezomib

[†]Patients ≥75 years may be immediately started on once-weekly regimen when initiating bortezomib
[‡]Bortezomib dose reductions: standard dose: 1.3 mg/m^2; dose reduced by 1 level: 1.0 mg/m^2; dose reduced by 2 levels: 0.7 mg/m^2
If sensory PN is associated with neuropathic pain, CTC score is upgraded one severity level.

Delforge et al. Lancet Oncol 2010; 11(11): 1086-1095
Mohty et al. Haematologica 2010; 95(2): 311-319
Sonneveld et al. Hematology Am Soc Hematol Educ Program 2010; 2010: 423-430

Summary

- **Once-weekly administration of bortezomib associated with**
  - **Similar efficacy as compared to twice-weekly administration in front-line treatment for elderly patients**
  - **Improved tolerability especially in terms of neurotoxicity**

Palumbo et al. J Clin Oncol 2010; 28: 5101-5109
Bringhen et al. Blood 2010; 116: 4745-4753
Mateos et al. Lancet Oncol 2010; 11: 934-941

A Phase 3 Prospective, Randomized, International Study (MMY-3021) Comparing Subcutaneous and Intravenous Administration of Bortezomib in Patients with Relapsed Multiple Myeloma

Philippe Moreau,[1] Halyna Pylypenko,[2] Sebastian Grosicki,[3] Evgeniy Karamanesht,[4] Xavier Leleu,[5] Maria Grishunina,[6] Grigoriy Rekhtman,[7] Zvenyslava Masliak,[8] Tadeusz Robak,[9] Anna Shubina,[10] Jean-Paul Fermand,[11] Martin Kropff,[12] James Cavet,[13] Dixie-Lee Esseltine,[14] Huaibao Feng,[15] Donna Skee,[15] Helgi van de Velde,[16] William Deraedt,[16] Jean-Luc Harousseau[17]

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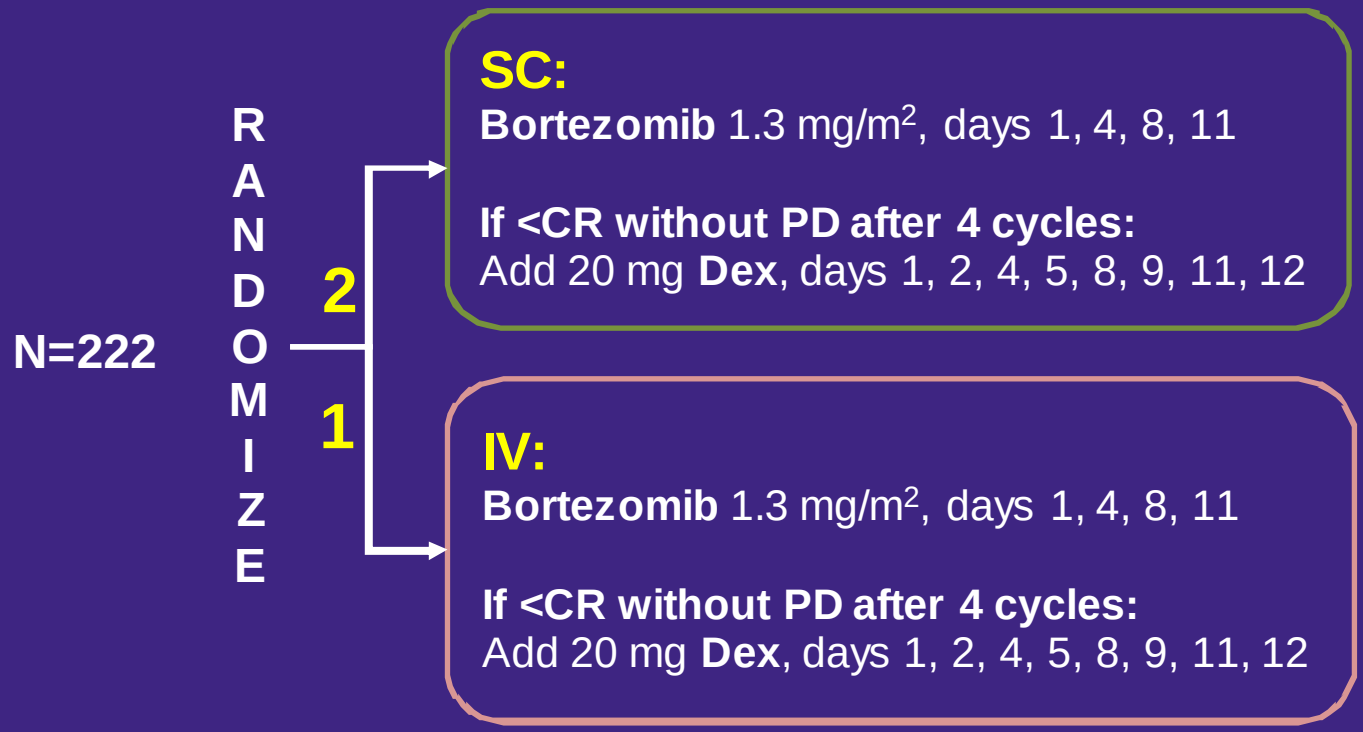
Study design



Eight 21-day cycles
(plus 2 cycles at end of cycle 8, if SD or PR as best response and evolving late PR or CR)

- **53 centers in 10 countries (Europe, Asia, South America)**
- **Non-inferiority design**
  - **60% retention of IV treatment effect as measured by ORR after 4 cycles**
  - **Stratification factors: ISS stage, number of prior lines of therapy (1 vs >1)**

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Bortezomib administration

IV injections

- **Administered at a concentration of 1 mg/mL as a 3- to 5-second IV push**
  - **3.5 mg in 3.5 mL normal [0.9%] saline**

SC injections

- **Administered at a concentration of 2.5 mg/mL**
  - **3.5 mg in 1.4 mL normal [0.9%] saline**
- **SC injection sites: thighs or abdomen**

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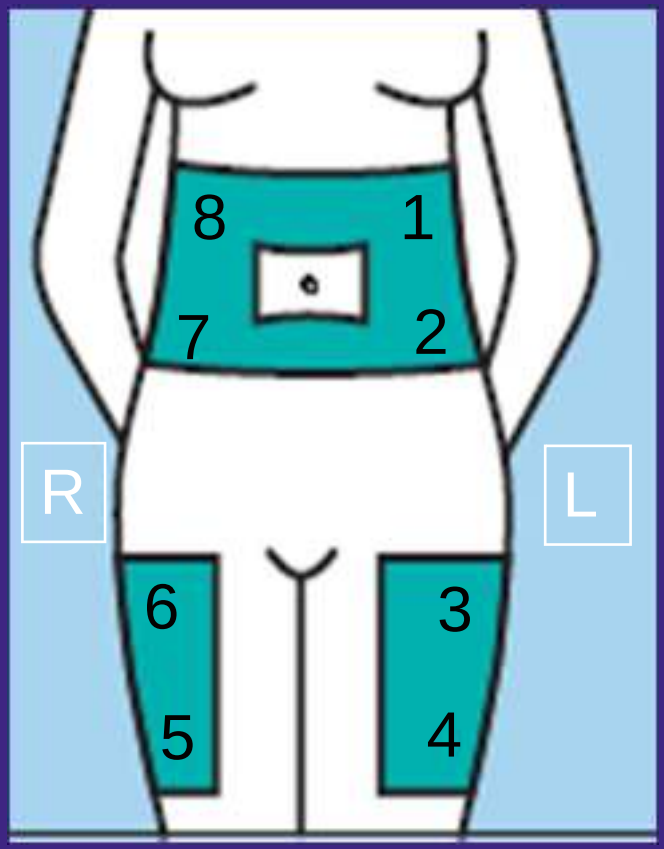
SC injection site rotation



Within the same cycle

- **Injections at same site were avoided**
- **Alternated between**
  - **right and left abdomen**
  - **upper and lower quadrant**

  or between
  - **right and left thigh**
  - **proximal and distal sites**

Moreau et al. Blood 2010; 116(21); Abstract 312 (oral presentation)

Patient demographics and baseline characteristics

Characteristic	Bortezomib IV (n=74)	Bortezomib SC (n=148)
Median age, yrs (range)	64.5 (38–86)	64.5 (42–88)
Aged ≥65 yrs, %	50	50
Male, %	64	50
White / Asian, %	96 / 4	97 / 3
Western / Eastern / Non-European, %	41 / 45 / 15	29 / 66 / 5
KPS 70% / 80% / ≥90%, %	16 / 32 / 51	22 / 39 / 40
1 / >1 prior lines of therapy, %*	65 / 35	62 / 38
ISS stage I / II / III disease, %*	27 / 41 / 32	27 / 41 / 32

*Stratification factor

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Response data

	Bortezomib IV (n=73)*	Bortezomib SC (n=145)*
Primary endpoint: response after 4 cycles (single agent bortezomib)		
ORR	42%	42%
CR	8%	6%
≥nCR	14%	12%
≥VGPR	16%	17%
Response after 8 cycles (bortezomib +/- dex)		
ORR	52%	52%
CR	12%	10%
≥nCR	22%	20%
≥VGPR	25%	25%

Comparable efficacy with SC and IV bortezomib administration

*n=4 not evaluable for response, n=3 in SC group, n=1 in IV group

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

Time to response, response duration, TTP, 1-year OS

	Bortezomib IV	Bortezomib SC	p
Median time to first response (months)*	1.4	1.4	
Median time to best response (months)*	1.5	1.6	
Median duration of response (months)	8.7	9.7	
TTP (months)	9.4	10.4	0.387
PFS (months)	8.0	10.2	0.295
1-year OS (%)	76.7	72.6	0.504

Comparable efficacy with SC and IV bortezomib administration

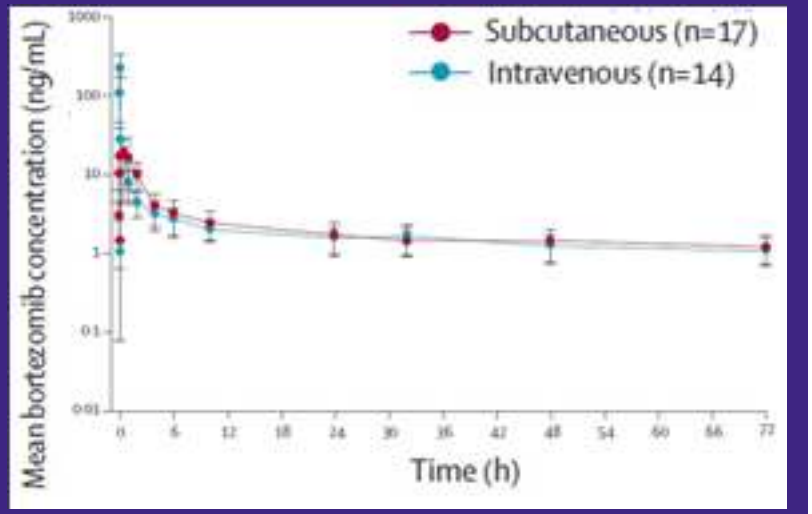
*In responding patients

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

Pharmacokinetic and pharmacodynamic parameters

	Bortezomib IV (n=14)	Bortezomib SC (n=17)
Pharmacokinetics		
C_{max} (ng/mL), mean (SD)	223 (101)	20.4 (8.87)
T_{max} (min), median (range)	2 (2–5)	30 (5–60)
AUC_{last} (ngxh/mL), median (range)	151 (42.9)	155 (56.8)
Pharmacodynamics		
E_{max} (%), mean (SD)	69.3 (13.2)	63.7 (10.6)
T_{emax} (min), median (range)	5 (2–30)	120 (30–1440)
AUE_{72} (%xh), mean (SD)	1383 (767)	1714 (617)

Plasma concentration-time profiles



- **Bortezomib systemic exposure equivalent between groups**
- **AUE_{72} similar in both groups**

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]
Moreau et al. Blood 2010; 116(21); Abstract 312 (oral presentation)

Adverse events (AEs)

	Bortezomib IV (n=74)	Bortezomib SC (n=147)
AEs, all grades, %	99	95
AEs, grade ≥3, %	70	57
Treatment-related AE, grade ≥3, %	55	39
Bortezomib dose reductions due to AEs, %	43	31
Discontinuations due to AEs, %	27	22

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

Adverse events (AEs)

Hematological

Grade ≥3, %	Bortezomib IV (n=74)	Bortezomib SC (n=147)
Anemia	8	12
Thrombocytopenia	19	13
Neutropenia	18	18
Leukopenia	7	6

Non-hematological

Grade ≥3, %	Bortezomib IV (n=74)	Bortezomib SC (n=147)
Peripheral sensory neuropathy	15	5
Neuralgia	9	3
Diarrhea	2	5
Vomiting	1	2
Constipation	1	1
Weight loss	1	0
Nausea	0	0
Asthenia	5	2
Fatigue	4	2
Pneumonia	8	5
Pyrexia	0	0

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

Peripheral neuropathy (PN)

	Bortezomib IV (n=74)	Bortezomib SC (n=147)	p-value*
Any PN event, %	53	38	0.044
Grade ≥2, %	41	24	0.012
Grade ≥3, %	16	6	0.026
Time to onset of PN, months	4.4	NE	
Cumulative dose at first onset of PN, mg/m^2	25.1	41.0	
Risk factors for PN, %			
Grade 1 PN at baseline	28	23	
Diabetes at baseline	11	13	
Exposure to prior neurotoxic agents	85	86	

Significantly fewer all-grade, grade ≥2 and grade ≥3 PN events with SC administration compared to IV administration

**P*-values based on 2-sided Fisher's exact test

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

Local injection site reactions

- **SC injection site reaction reported as an AE**
  - **At least one reaction in 6%**
  - **Bortezomib dose modification in 1%**
- **Detailed local injection site questionnaire:**
  - **Most common reaction: redness in 57%**
  - **1% of patients with severe injection site reactions**
  - **Median time to resolution: 6 days (100% resolved)**

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

Summary

- **Efficacy of bortezomib similar by SC and IV administration in patients with relapsed MM**
  - **Similar PK (systemic exposure) and PD (proteasome inhibition) profiles with IV and SC administration**
- **SC administration appeared to have an improved safety profile compared with IV administration**
  - **Significantly fewer all-grade, grade ≥2, and grade ≥3 PN events with SC administration compared to IV administration**
- **SC administration had acceptable local tolerability**

Moreau et al. Lancet Oncol 2011 [Epub ahead of print]

Feasibility of bortezomib home administration: experience from pilot studies

- **UK[1]:** 9 patients (60-86 years), relapsed MM
  - No infusion reactions, no adverse reactions during administration
  - Feasible in elderly, heavily pretreated, with comorbidities
- **Ireland[2]:** 23 patients, newly diagnosed (transplant setting) and relapsed MM
  - No significant complications
  - Responses as expected with standard administration
  - Patient feedback: convenient, minimum negative impact on QoL
- **Belgium MyCare@home program[3]:** 17 patients (mean 69.4 years), relapsed MM
  - No impact on treatment efficacy or safety
  - Longer treatment duration, fewer dose reductions and drug-related AEs
  - Program extended to 200 patients

[1]*Hammond et al. Clin Lymphoma Myeloma 2009; 9 (Suppl 1): S21 (Abstract 133)*

[2]*Meenaghan et al. Eur J Oncol Nurs. 2010;14(2):134-136*
[3]*Delforge et al. Manuscript in preparation*

Overall summary

- **How to optimize bortezomib administration?**
  - **Once-weekly dosing[1-3]**
  - **Subcutaneous vs intravenous[4]**
- **What are the implications?**
  - **Similar efficacy[1-4]**
  - **Better tolerability with significantly lower neurotoxicity[1-4]**
- **Possible applications?**
  - **Elderly and less mobile patients**
  - **Prolonged treatment including maintenance**
  - **Comorbidities e.g. neuropathy**

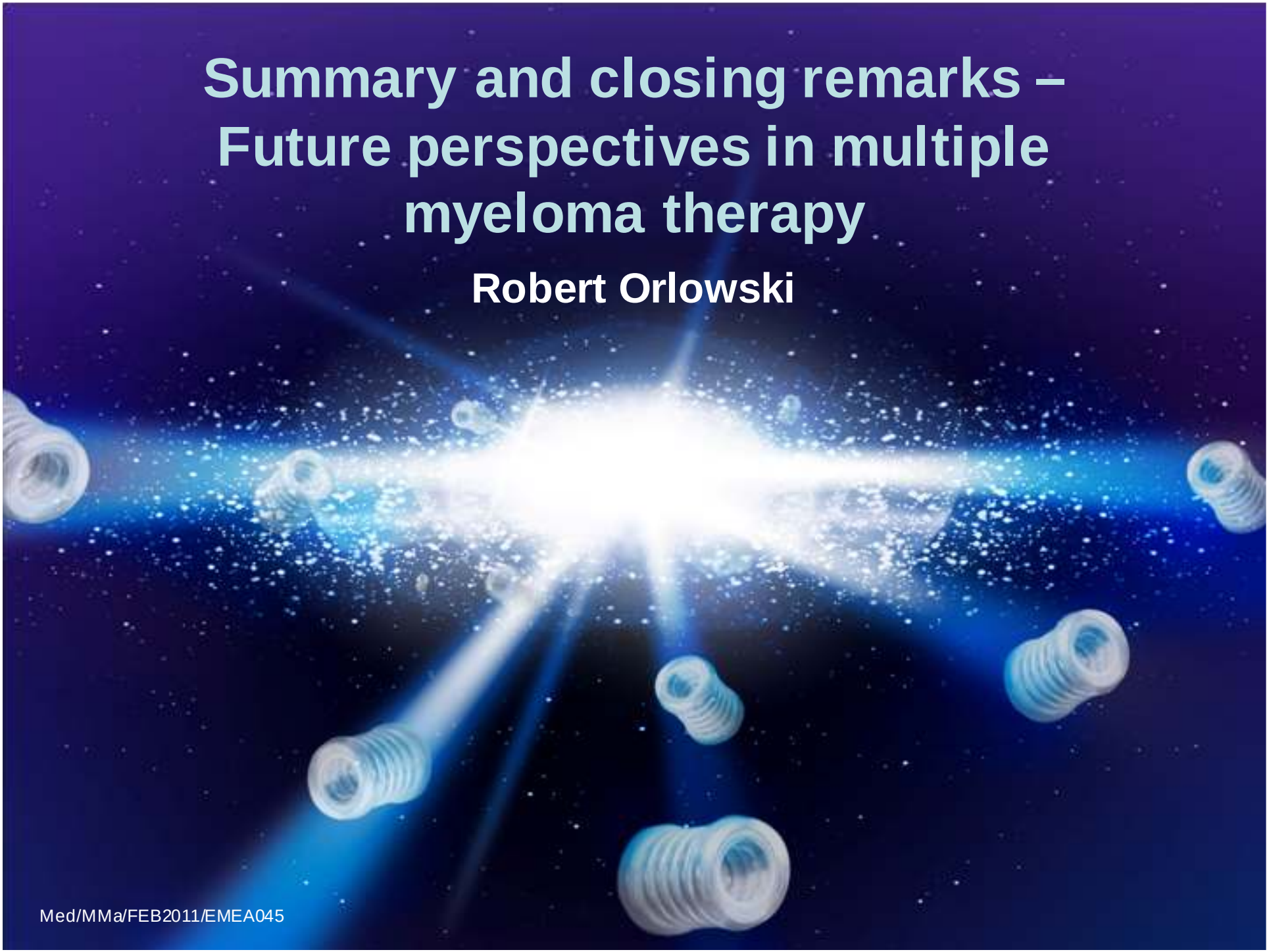
[1]*Palumbo et al. J Clin Oncol 2010; 28: 5101-5109*
[2]*Bringhen et al. Blood 2010; 116: 4745-4753*
[3]*Mateos et al. Lancet Oncol 2010; 11: 934-941*
[4]*Moreau et al. Lancet Oncol 2011 [Epub ahead of print]*


Optimizing Patient Outcomes Through Individualized Treatment Approaches: Phase III Data
Co-Chairs: Robert Orlowski, USA and
Pieter Sonneveld, The Netherlands
Med/MMa/FEB2011/EMEA045


Panel discussion
Moderated by Co-Chairs

Summary and closing remarks – Future perspectives in multiple myeloma therapy

Robert Orlowski



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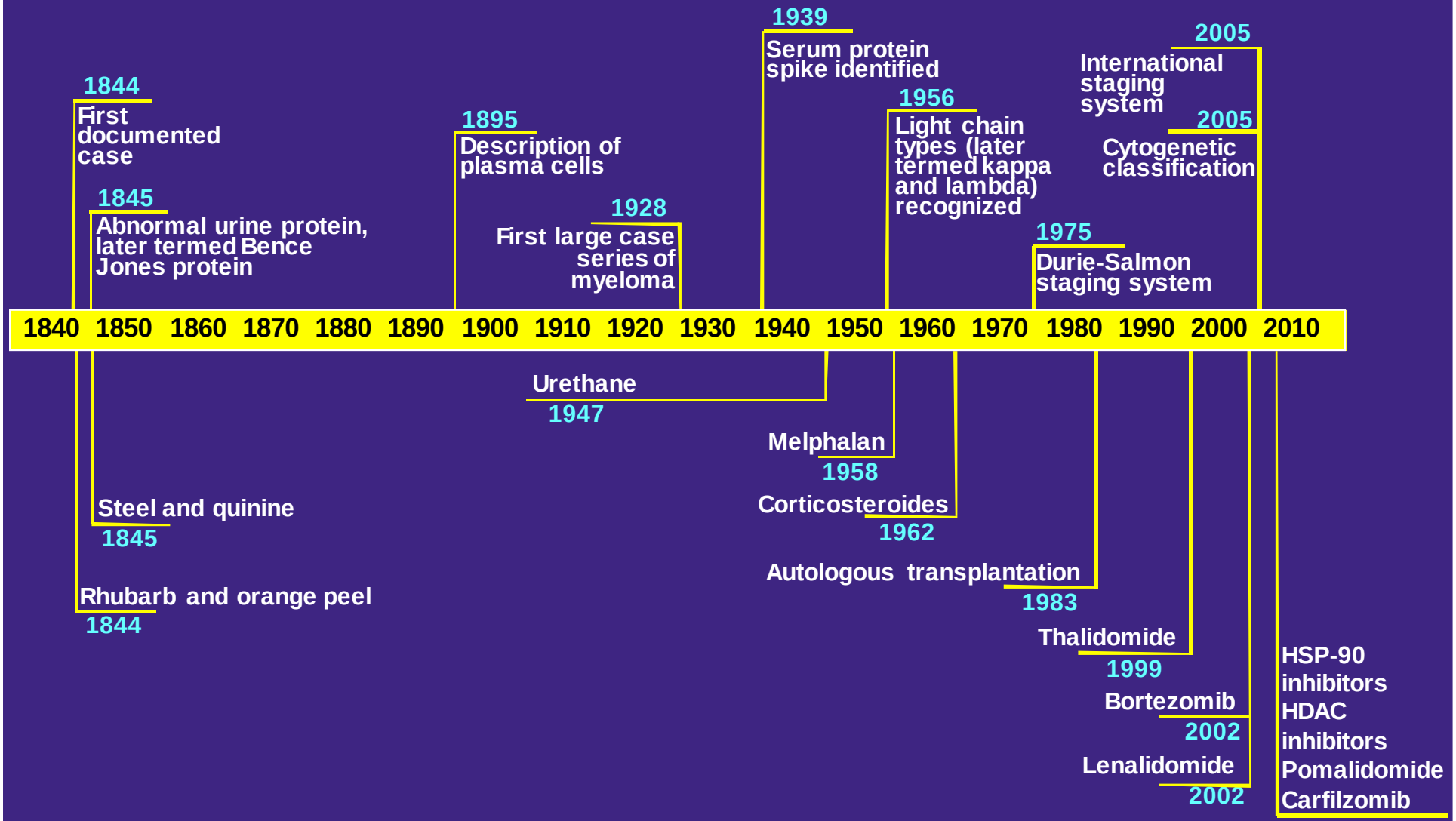
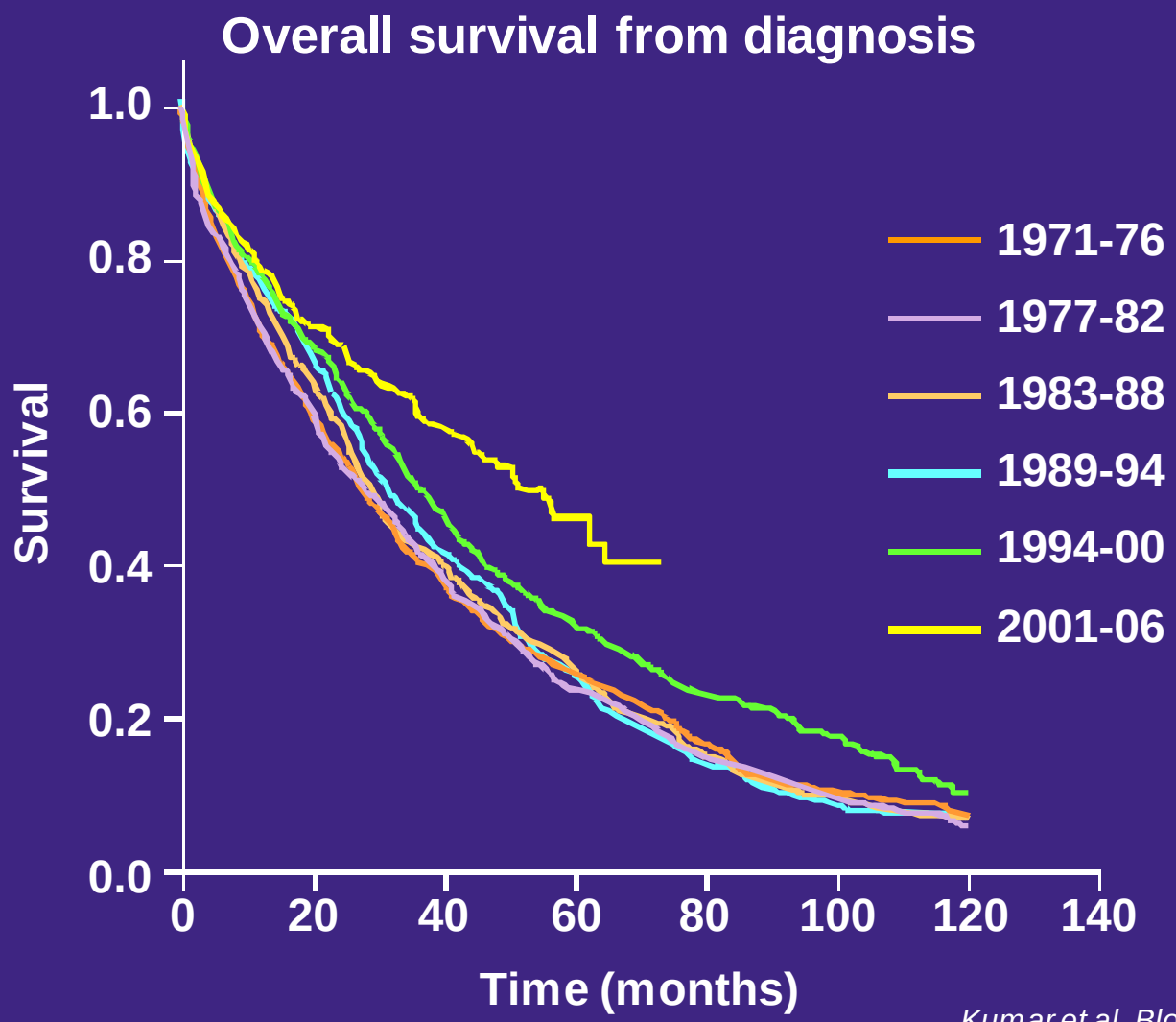
Evolution of myeloma therapy



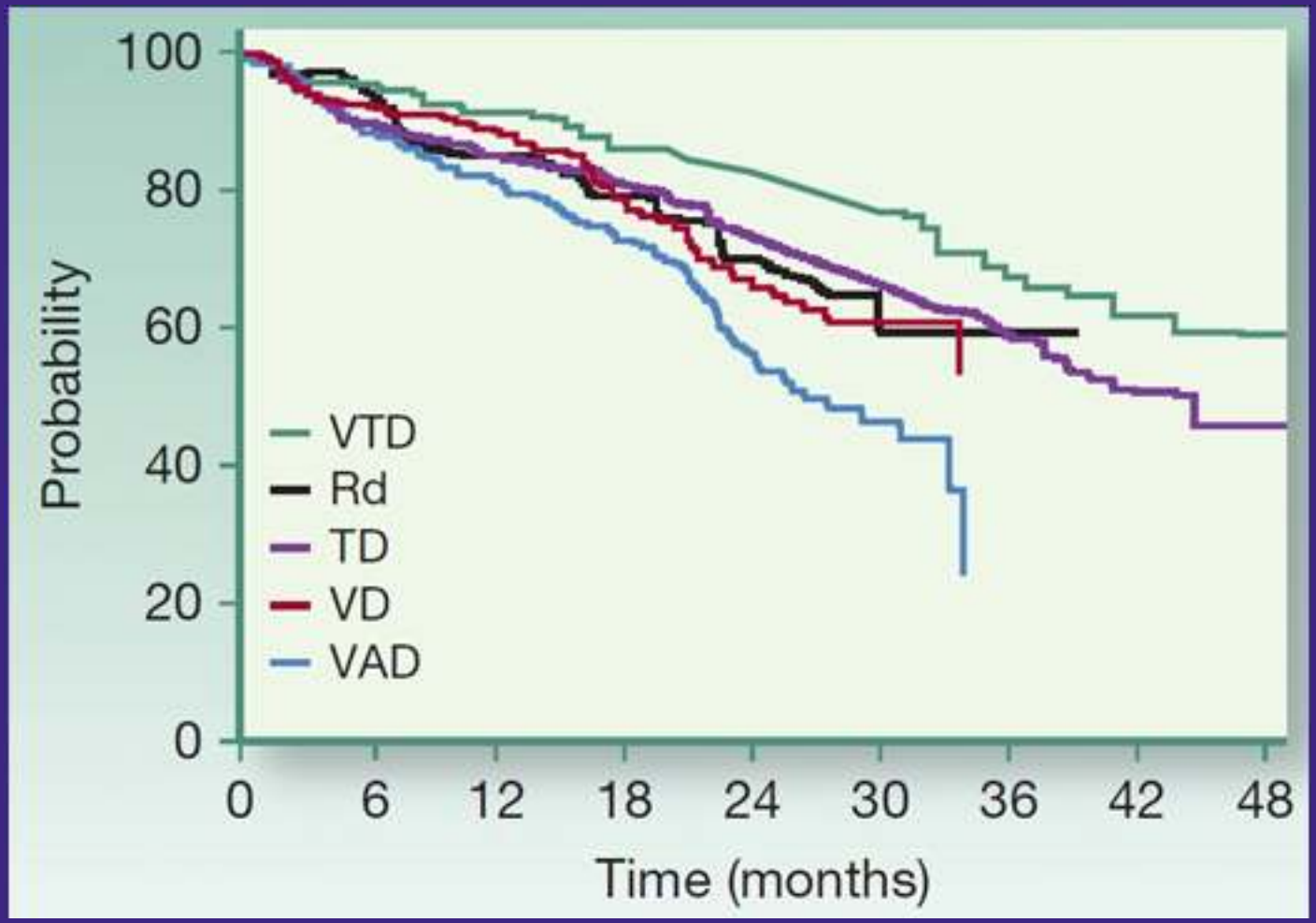
Adapted from: Kyle and Rajkumar. Blood 2008; 111(6): 2962-2972

Impact of novel agents up-front



Kumar et al. Blood 2008; 111(5): 2516-2520

PFS improvement: Transplant eligibles



Palumbo et al. Clin Cancer Res 2011; 17(6): 1253-1263

Transplant-ineligible population

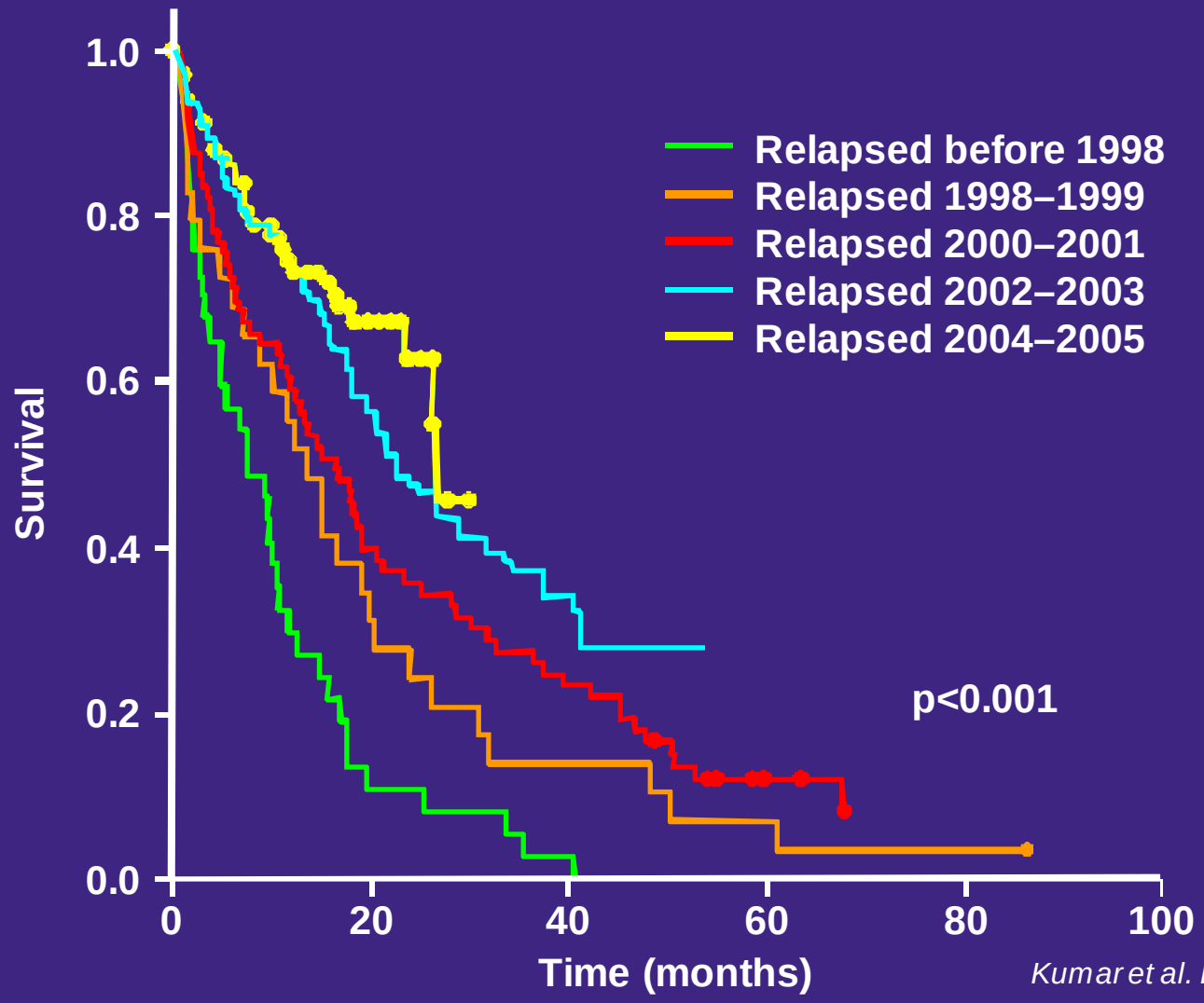
	Median PFS (months)	3-year OS (%)	Median OS (months)
MP[1-4,7,9]	11–18.5	~40–60*	29.1–49.4
MPT[1-6]	15–27.5	~45–65*	29–51.6
VMP[7,8,11]	21.7–27.4	68.5†	Not reached @ 36.7 months†
MPR-R[9]	31	N/A	N/A
VMP-VT/VP[10]	34	74	Not reached @ 32 months
VMPT-VT[11]	37.2	85	Not reached @ 32 months

*Estimates from OS curves; N/A: not available

†3-year OS data reported; 5-year OS data analysis ongoing

[1]Palumbo et al. Blood 2008; 112: 3107–3114
[2]Facon et al. Lancet 2007; 370: 1209–1218
[3]Hulin et al. J Clin Oncol 2009; 27: 3664-3670
[4]Waage et al. Blood 2010; 116: 1405-1412
[5]Wijermans et al. J Clin Oncol 2010; 28: 3160-3166
[6]Beksac et al. Eur J Haematol 2011; 86: 16-22
[7]San Miguel et al. N Engl J Med 2008; 359(9): 906–917; Supplementary Appendix
[8]Mateos et al. J Clin Oncol 2010; 28(13): 2259-2266
[9]Palumbo et al. ASH 2010; Abstract 622 (oral presentation)
[10]Mateos et al. Lancet Oncol 2010; 11(10): 934-941
[11]Palumbo et al. ASH 2010; Abstract 620 (oral presentation)

Impact of novel agents at relapse

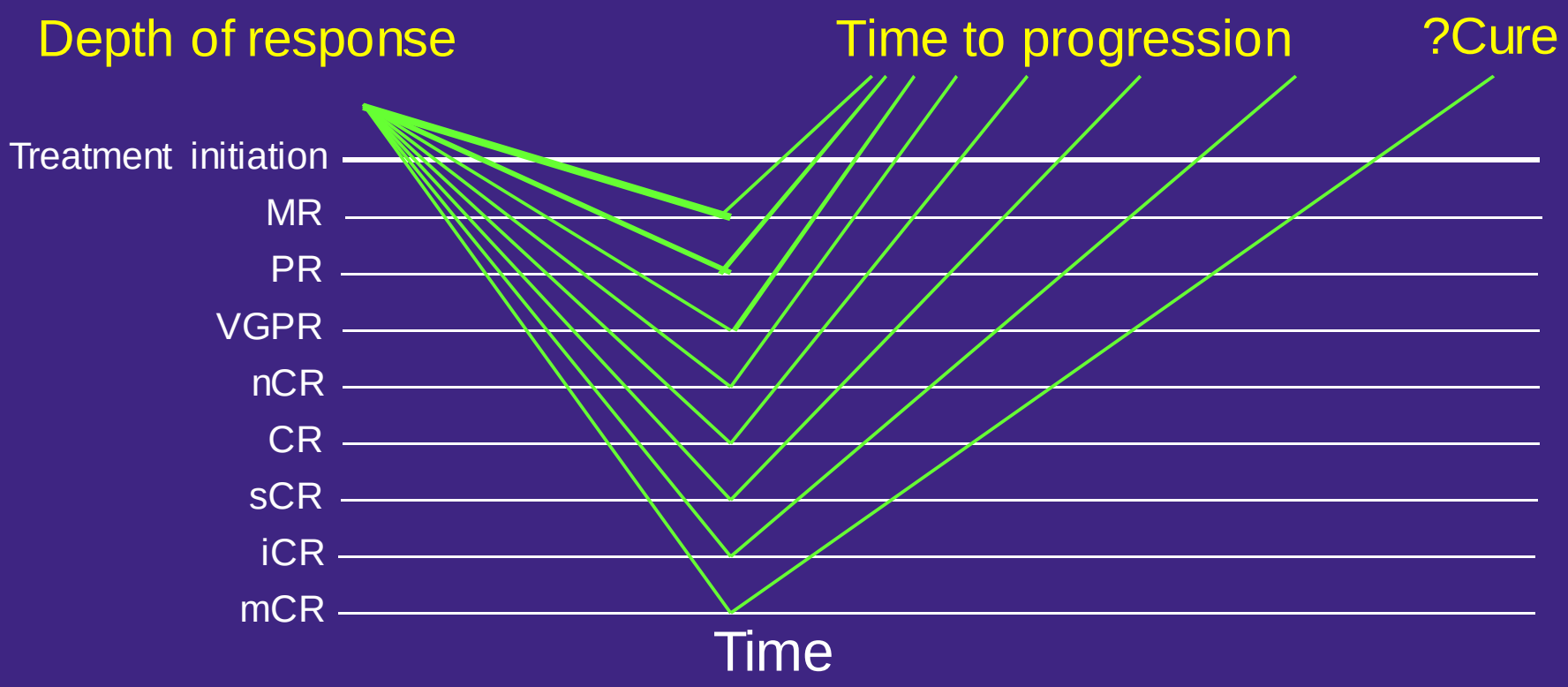


Kumar et al. Blood 2008; 111(5): 2516-2520

A cornucopia of new drugs

- New small molecules
  - Novel signal transduction inhibitors
  - Second generation proteasome inhibitors
  - Second & third generation immunomodulators
  - Histone deacetylase & heat shock protein 90 inhibitors
- Monoclonal antibodies
  - Siltuximab
  - Elotuzumab
  - Lorvotuzumab mertansine

Is cure within reach?



- **Will molecular remission equal cure ?**

Niesvizky et al. Br J Haematol 2008; 143(1): 46-53; Harousseau et al. Blood 2009; 114(15): 3139-3146
Chanan-Khan et al. J Clin Oncol 2010; 28(15): 2612-2624

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