Key Clinical & Scientific Abstracts from ASH 2010

Dr. Rakesh Popat
St. Bartholomew's Hospital
London

ASH Day 1

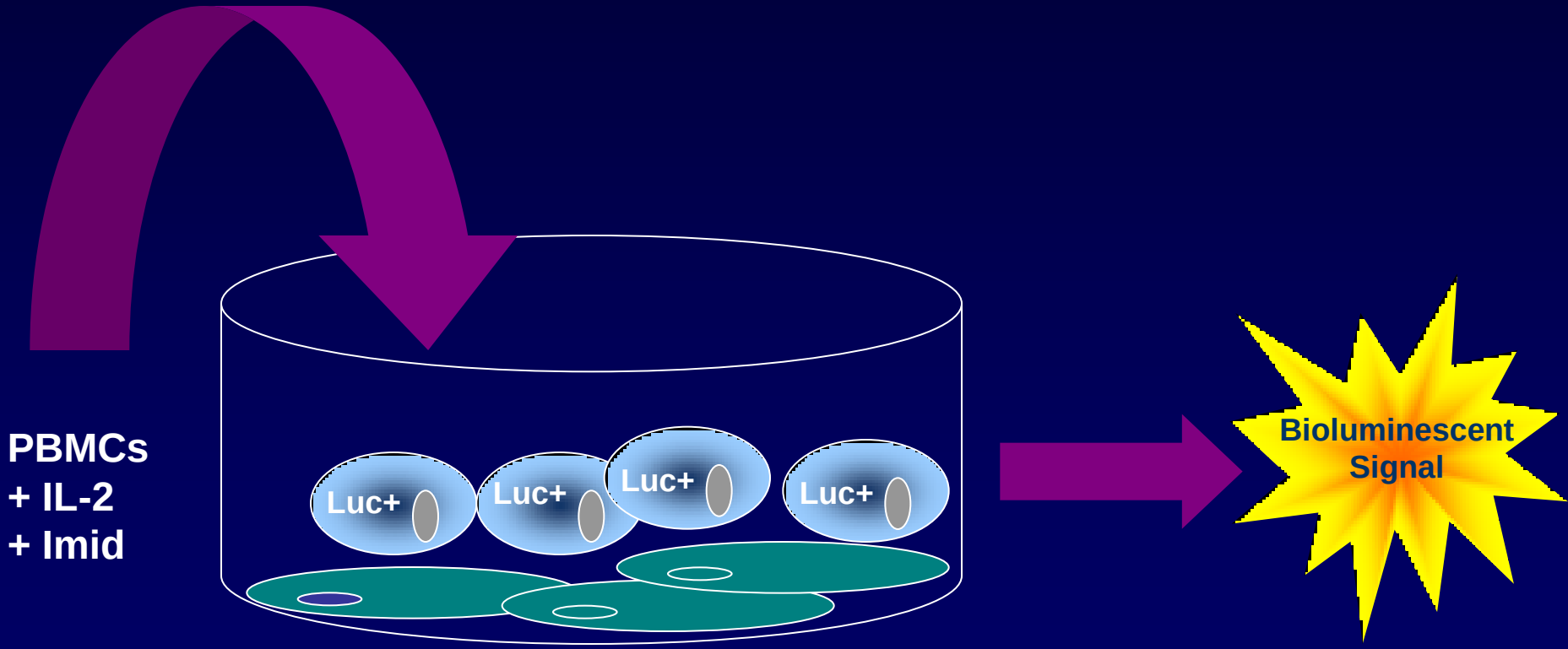
Overview

- Science:
  - High throughput novel drug assays
  - Genomics:
    - Bortezomib response
    - Neuropathy
- Cytogenetic Risk:
  - Italian (Cavo)
  - Spanish (Mateos)
  - Dutch/German (Sonneveld)
- Phase III Clinical Trials:
  - Front line combination lenalidomide therapy in elderly patients
  - s.c. bortezomib
- Others

Compartment-Specific Bioluminescence Imaging Platform for the Open-Ended Identification of Novel Immunomodulatory Agents and High-Throughput Evaluation of Anti Tumor Immune Function

Douglas W. McMillin, Jake Delmore, Matthew W. Vanneman, Robert L. Schlossman, John Feather, Nikhil C. Munshi, Jacob P. Laubach, Paul G Richardson, Glenn Dranoff, Kenneth C. Anderson, and Constantine S. Mitsiades

Methods



384 well plate

Relevance

- Allows high through-put screening
- Includes stromal interactions
- Luc+ cells only assessed
- Immunomodulatory effects may be investigated:
  - PBMCs enhanced with lenalidomide & pomalidomide whilst inhibited with Dexamethasone
- CD56+ cells have higher anti-myeloma activity than unselected PBMCs
- Screening for novel Imids

Improved Outcome with Total Therapy 3 (TT3) Can Be Traced to GEP70-Defined High-Risk Disease with Trisomy of 1q21 and Modest Hyper-Activation of PSMD4

John Shaughnessy, Jr., Pingping Qu, Erming Tian, Bijay Nair, Sarah Waheed, Yazan Alsayed, Frits van Rhee, John Crowley, and Bart Barlogie

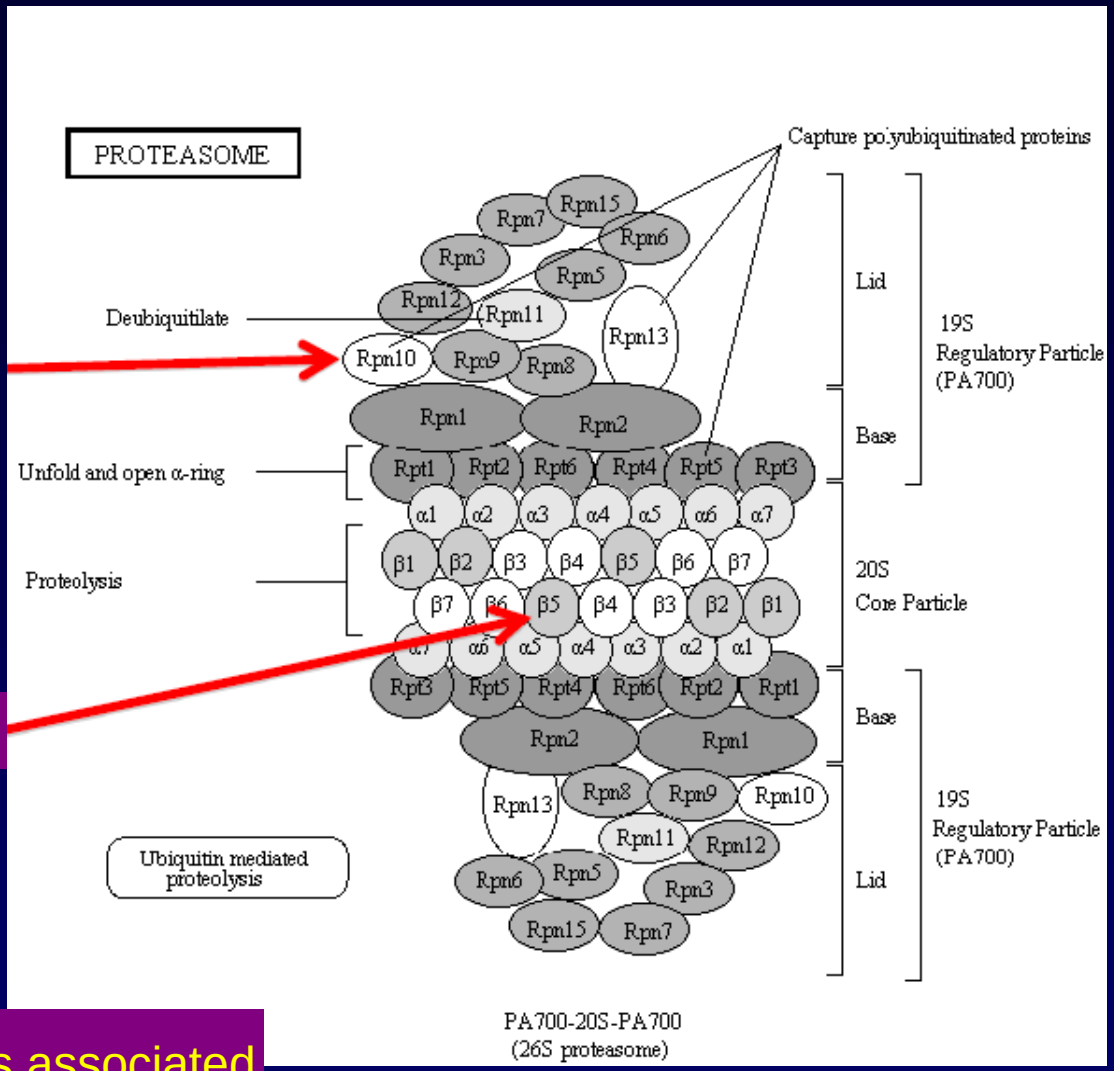
Background

- 70 gene model predicts high risk disease in approx 15% of newly diagnosed patients
- Driven by copy number sensitive gains in 1q21
- Candidate genes within amplificon:
  - IL6R, MCL1, BCL9
  - CKS1B, PSMD4

Shaughnessy *et al.* ASH 2010

PSMD4

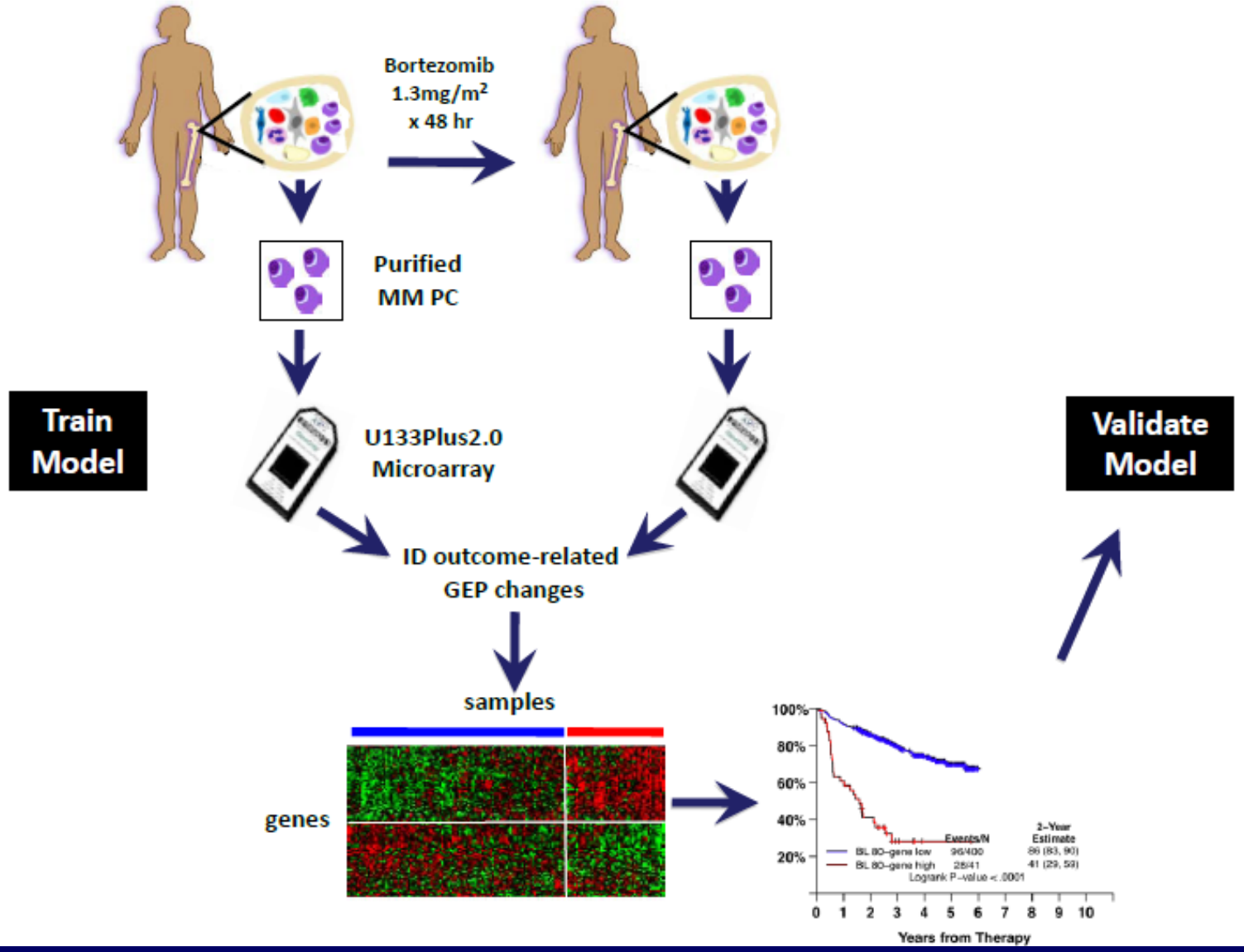
PSMB5



Point mutations associated with resistance to proteasome inhibition

Shaughnessy *et al.* ASH 2010

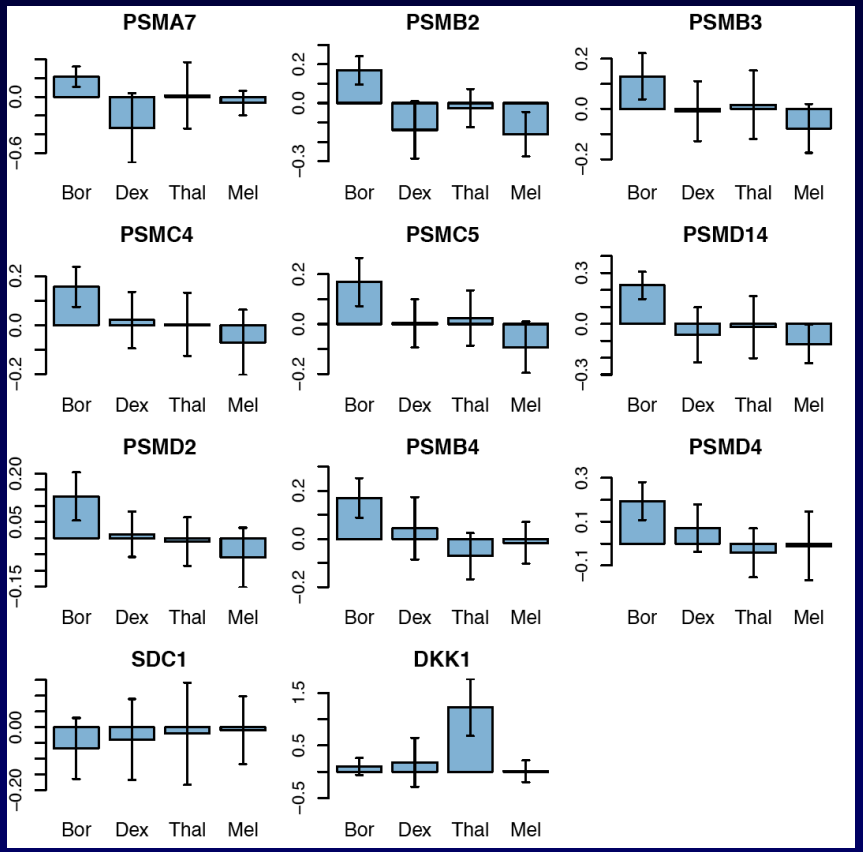
Strategy Used to Develop and Validate post-BOR PGx Model



Shaughnessy *et al.* ASH 2010

Results

- Post bortezomib high risk GEP characterised by increase in proteasome genes
- Significant over-representation of 26 proteasome genes in high risk gene model

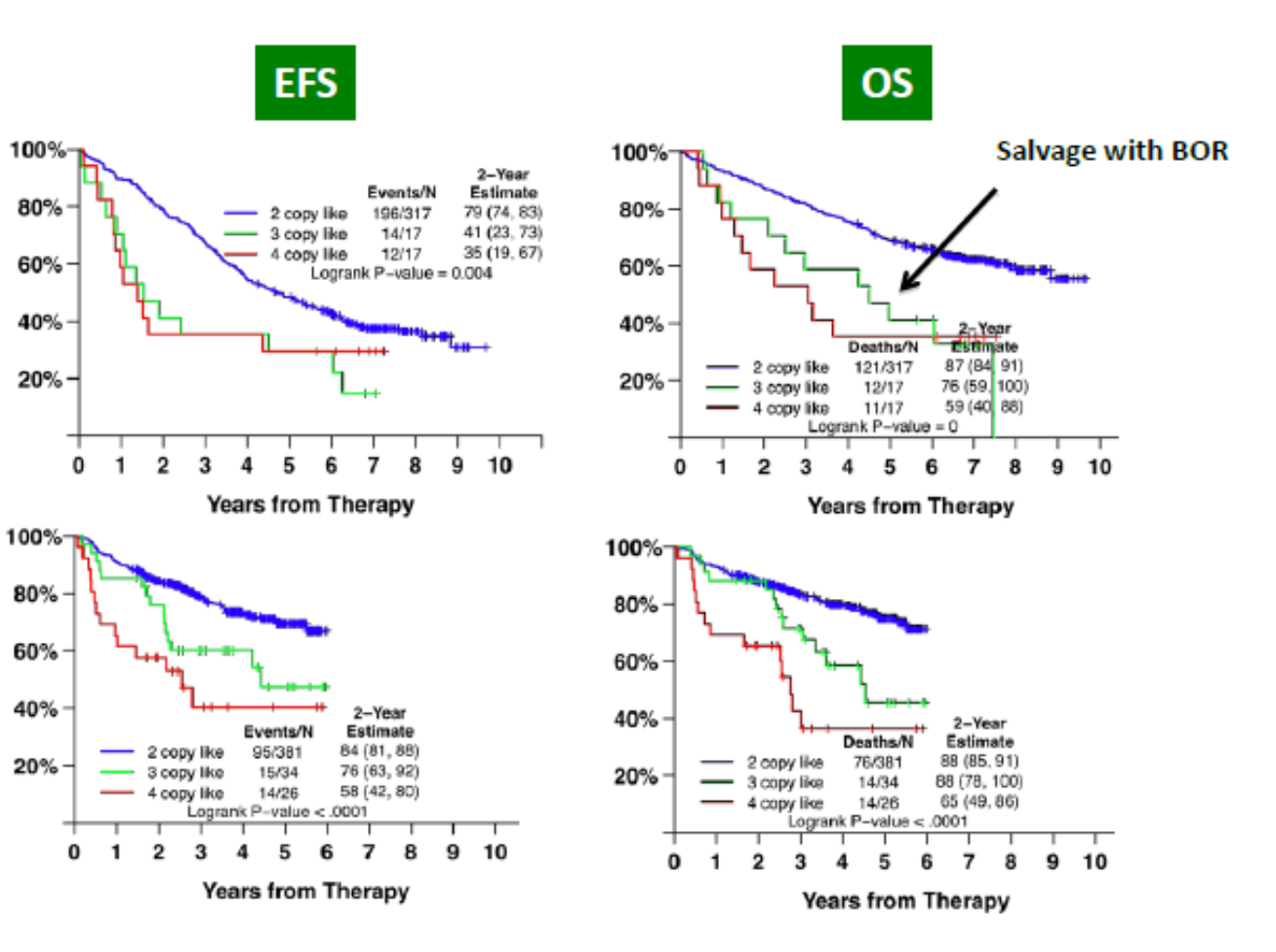


Shaughnessy *et al.* ASH 2010

3-copy-like PSMD4 Expression Linked to Improved Outcome in TT3 but not TT2

TT2

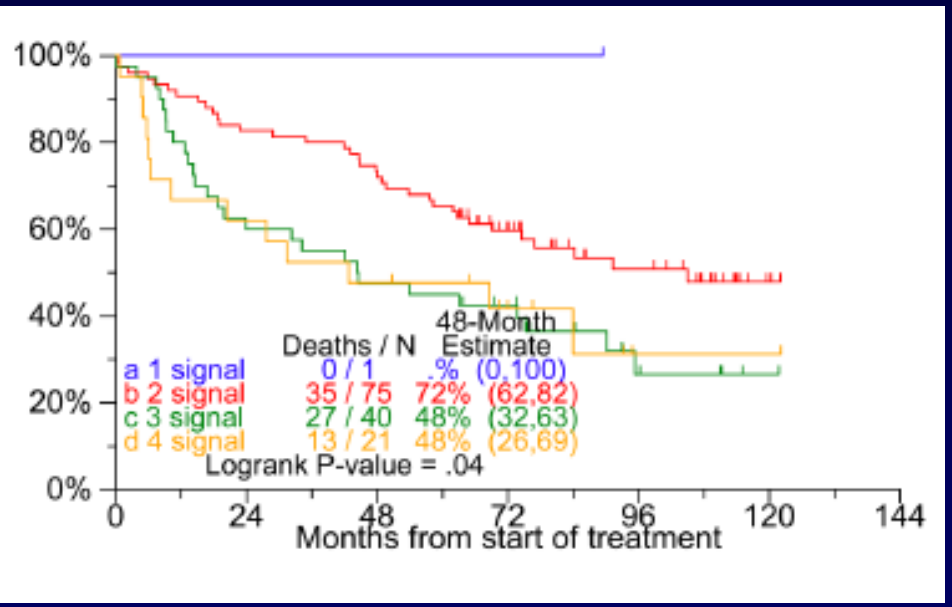
TT3



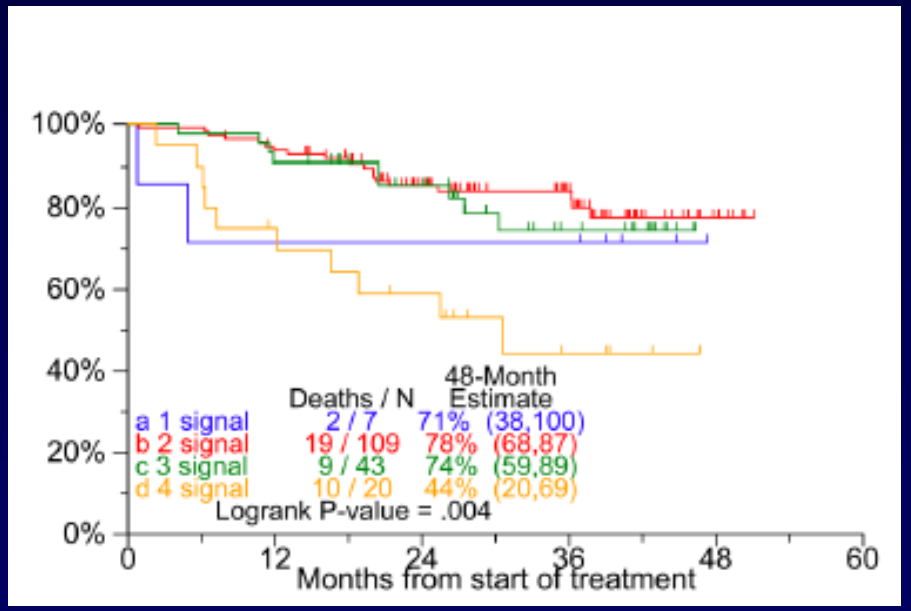
Shaughnessy *et al.* ASH 2010

Bortezomib overcomes High Risk Associated with 3, but not 4 copies of 1q21 Defined by TRI-FISH

TT2



TT3



Shaughnessy *et al.* ASH 2010

Conclusions

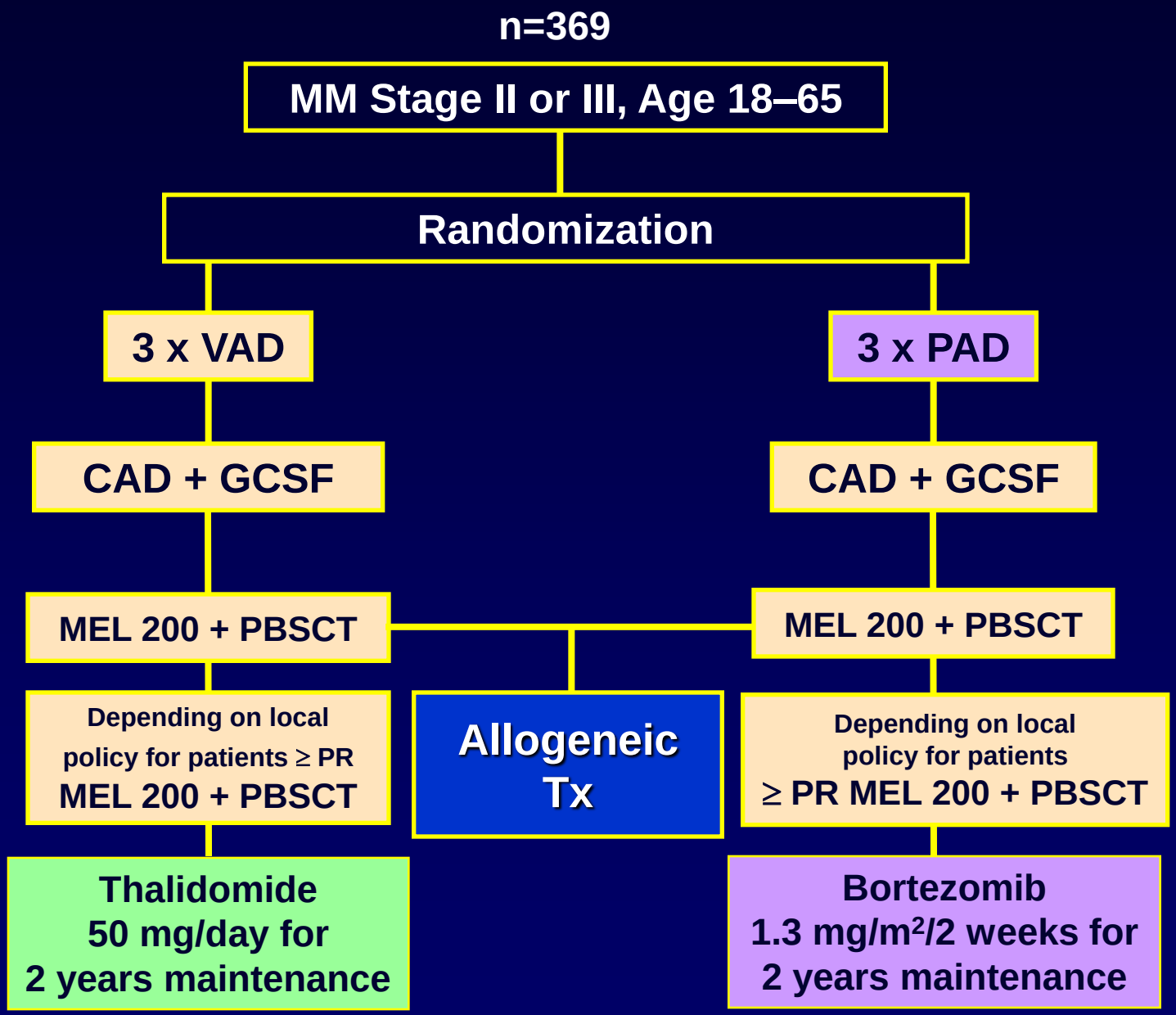
- GEP changes following a test dose of bortezomib are linked to survival
- Post bortezomib high risk signature associated with increase in proteasomal genes
- Improved outcome with TT3 can be correlated with expression of proteasomal genes. High is bad!
- Proteasomal hyperactivity possibly related to increase copy number of PSMD4 at 1q21 may determine sensitivity to bortezomib

Shaughnessy *et al.* ASH 2010

Development of Bortezomib Induced Peripheral Neuropathy (BiPN) In Multiple Myeloma: Incidence and Molecular Characterization In Newly Diagnosed Patients Treated with Bortezomib

Annemiek Broyl, Sophie Corthals, Joost L.M. Jongen, Bronno van der Holt, Rowan Kuiper, Yvonne de Knegt, Laila el Jarari, Uta Bertsch, Henk Lokhorst, Brian GM Durie, Hartmut Goldschmidt, and Pieter Sonneveld

HOVON 65 MM / GMMG-HD4



Methods

- Genetic variation analyzed using a custom-built SNP chip (BOAC)
- 3404 SNPs selected in "functional regions" within 983 genes
- Represent cellular functions and pathways.
- Gene expression profiles analyzed in purified myeloma plasma cells using Affymetrix 133 Plus 2.0 array
- Integration of GEP with SNP profiles to make an association profile

Neuropathy Rates

	Bortezomib-based induction treatment (n=250)	Vincristine-based induction treatment (n=250)	p value
Baseline peripheral neuropathy	8 (3%)	13 (5%)	0·37
Peripheral neuropathy after one cycle			
Grade 2–4	20 (8%)	11 (4%)	0·27
Grade 2	10 (50%)	9 (82%)	..
Grade 3	7 (35%)	1 (9%)	0·18*
Grade 4	3 (15%)	1 (9%)	..
Peripheral neuropathy after two or three cycles			
Grade 2–4	63 (25%)	17 (7%)	<0·0001
Grade 2	31 (49%)	11 (65%)	..
Grade 3	24 (38%)	6 (35%)	0·72*
Grade 4	8 (13%)	0	..

Broyl *et al.*, ASH 2010

Results

- Early-onset bortezomib-induced neuropathy
  - GEP: transcription, apoptosis, AMPK signalling
  - SNP: caspase-9, splicing regulation of NEK4, DNA repair and nervous system development and function

Broyl *et al.*, ASH 2010

Results

- Late onset bortezomib-induced neuropathy:
  - GEP: Development and function of the nervous system (SOD2 and diabetic neuropathy)
  - SNP: SERPINs BRCA1

Broyl *et al.*, ASH 2010

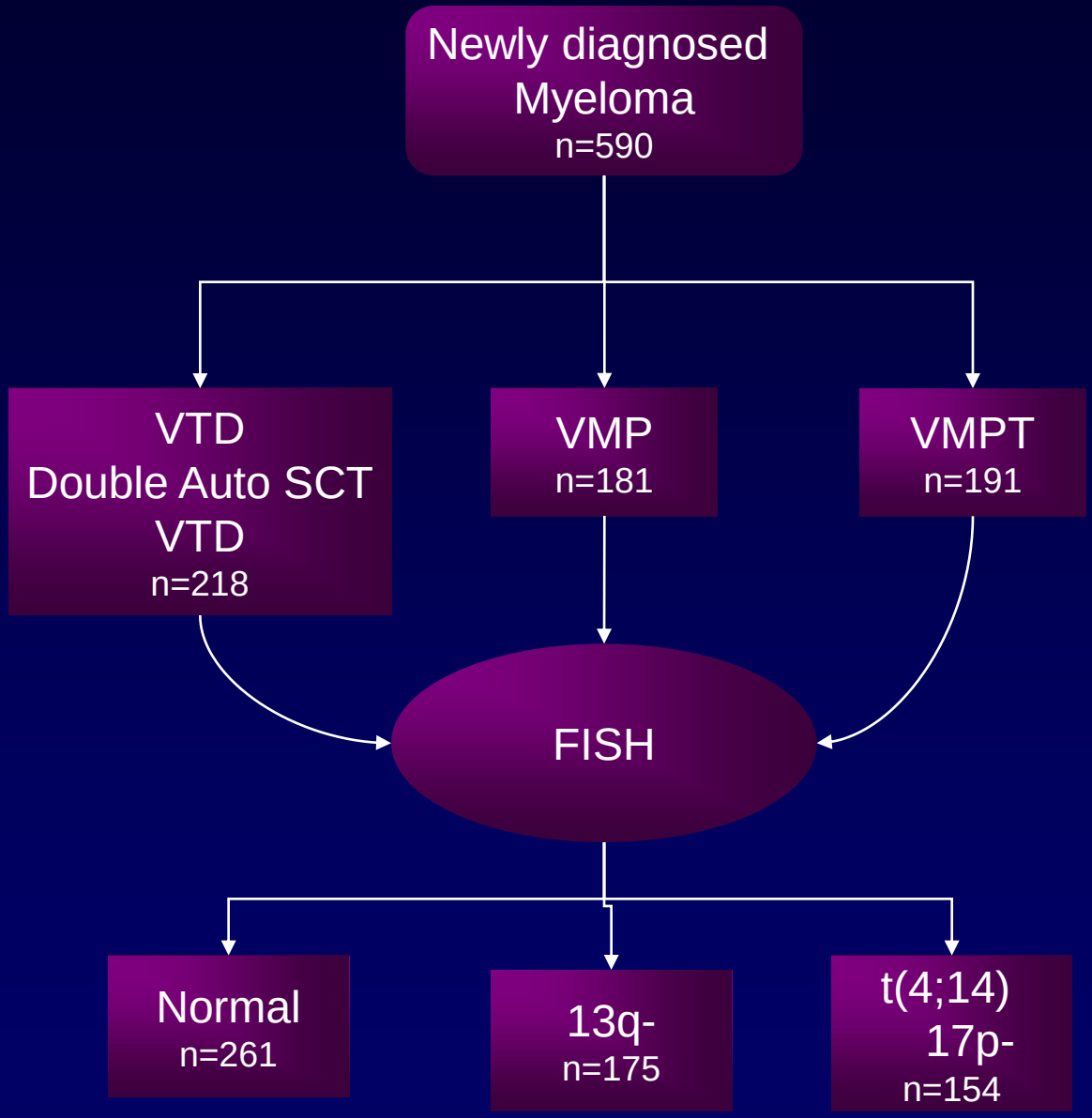
Conclusions

- Contribution of host and myeloma upon development of neuropathy
- Early: apotosis
- Late: inflammation & DNA repair
- Different results for bortezomib and vincristine

Broyl *et al.*, ASH 2010

Bortezomib-Based Induction Treatments Improve Outcomes of Newly Diagnosed Multiple Myeloma Patients with High-Risk Cytogenetic Abnormalities

Michele Cavo, Sara Bringhen, Carolina Terragna, Paola Omedè, Giulia Marzocchi, Marina Ruggeri, Sandra Durante, Maria Teresa Petrucci, Tommasina Guglielmelli, Giulia Benevolo, Vittorio Montefusco, Franco Narni, Antonietta Falcone, Catello Califano, Anna Baraldi, Silvana Pasini, Piero Galieni, Fortunato Morabito, Mariella Grasso, Daniela Gottardi, Vincenzo Rizzo, Mario Boccadoro, Nicoletta Testoni, and Antonio Palumbo



Cavo *et al.*, ASH 2010

Results

1. Del(13q) alone had no adverse effect on PFS and OS
2. Presence of t(4;14) and/or del(17p) did not adversely influence PFS, but associated with a shorter OS, due at least in part to a worse outcome after relapse
3. del(17p) alone did not predicted for shorter PFS and OS compared with t(4;14), possibly as a result of the relatively long-term exposure to bortezomib
4. the presence of both del(17p) and t(4;14) was likely to confer a particularly dismal clinical outlook

Cavo *et al.*, ASH 2010

VMP vs VTP followed by VT or VP maintenance

- VMP vs VTP
- Maintenance arm: Vt vs VP
- FISH available in 231 patients
- High risk (n=44): t(4;14) t(14;16) 17p-
- Standard risk (n=187): without CA
- CR: 21% vs 27%
- But shorter PFS and OS in high risk irrespective of induction or maintenance arms
- Bortezomib in this regimen did not help poor risk

Mateos *et al*., ASH 2010

HOVON-65/GMMG-HD4 Trial: PAD vs VAD

n=833	PFS/m		3 year OS	
	VAD	PAD	VAD	PAD
t(4:14)	18	36	39%	76%
1q21	22	30	59%	83%
17p-	13	26		

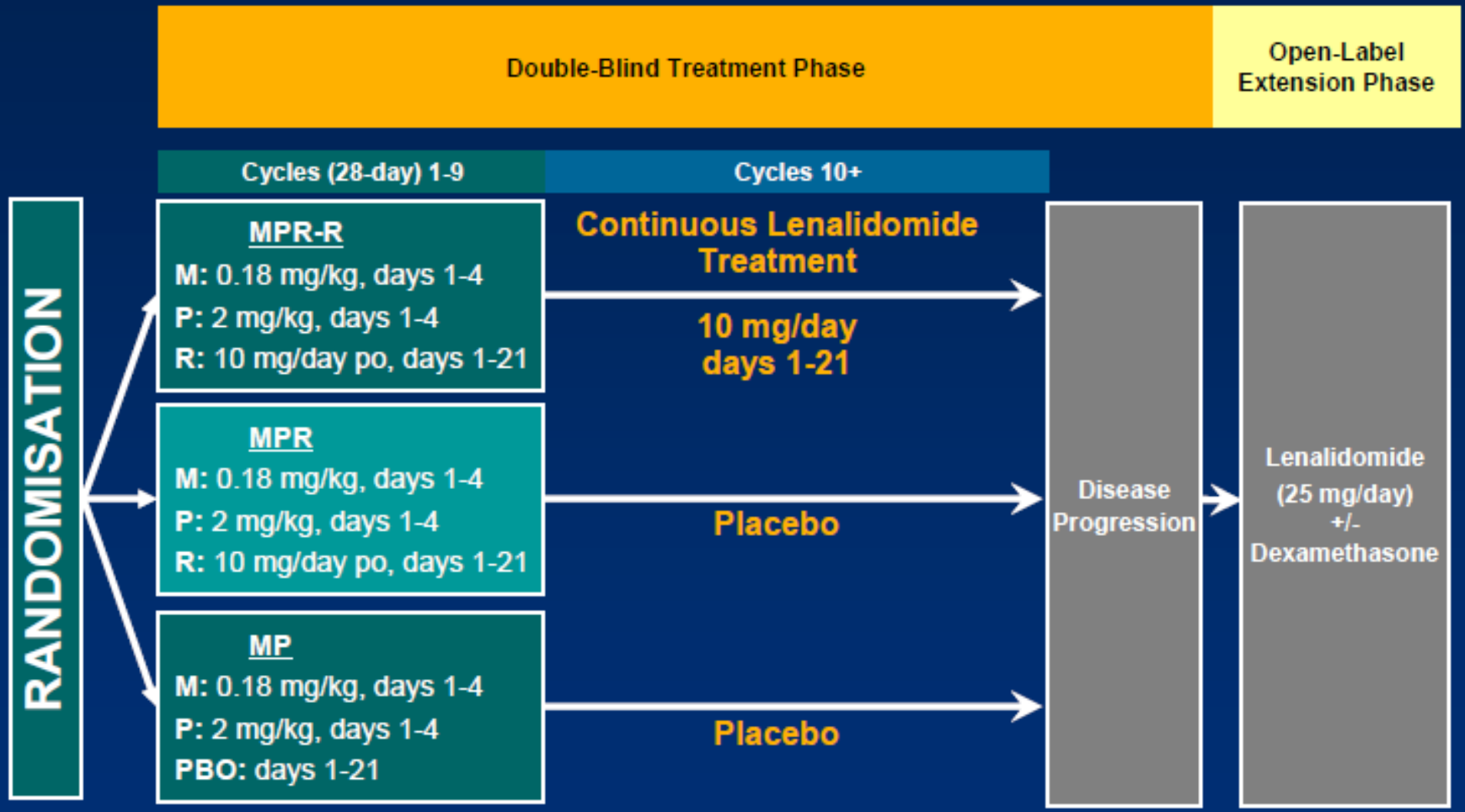
Improvement in t(4;14), partial improvement in 1q21, poor outcome with 17p-

A Phase 3 Study Evaluating the Efficacy and Safety of Lenalidomide Combined with Melphalan and Prednisone In Patients ≥65 Years with Newly Diagnosed Multiple Myeloma (NDMM): Continuous Use of Lenalidomide Vs Fixed-Duration Regimens

Antonio Palumbo, Michel Delforge, John Catalano, Roman Hajek, Martin Kropff, Maria Teresa Petrucci, Zhinuan Yu, Lindsey Herbein, Jay M. Mei, Christian J. Jacques, and Meletios A. Dimopoulos

Phase III Study Schema

N = 459, 82 centers in Europe, Australia, and Israel



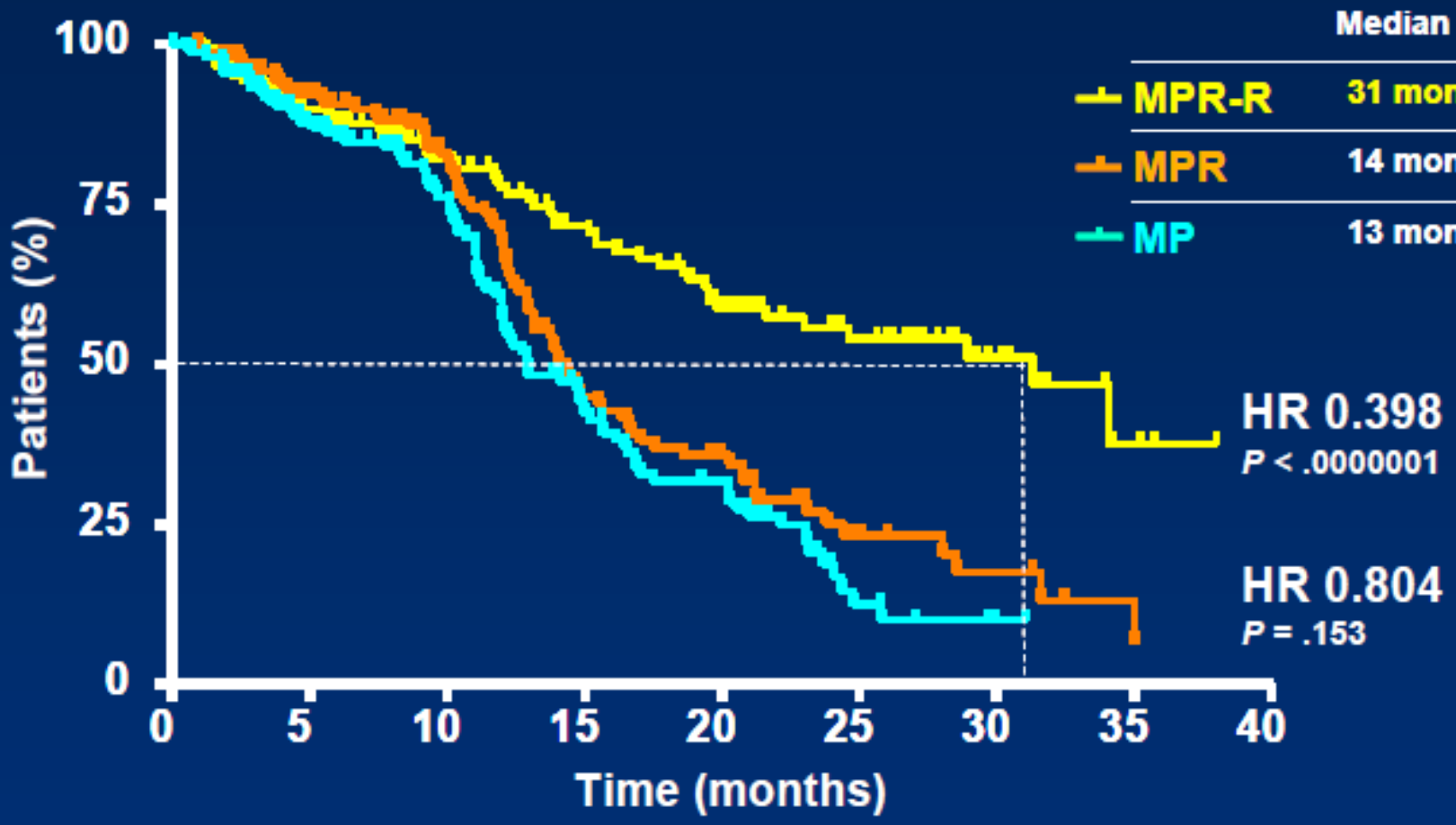
Stratified by age (≤ 75 vs > 75 years) and stage (ISS I/II vs III)

M, melphalan; P, prednisone; R, lenalidomide; PBO, placebo; po, orally; ISS, International Staging System.

Progression-Free Survival*

All Patients

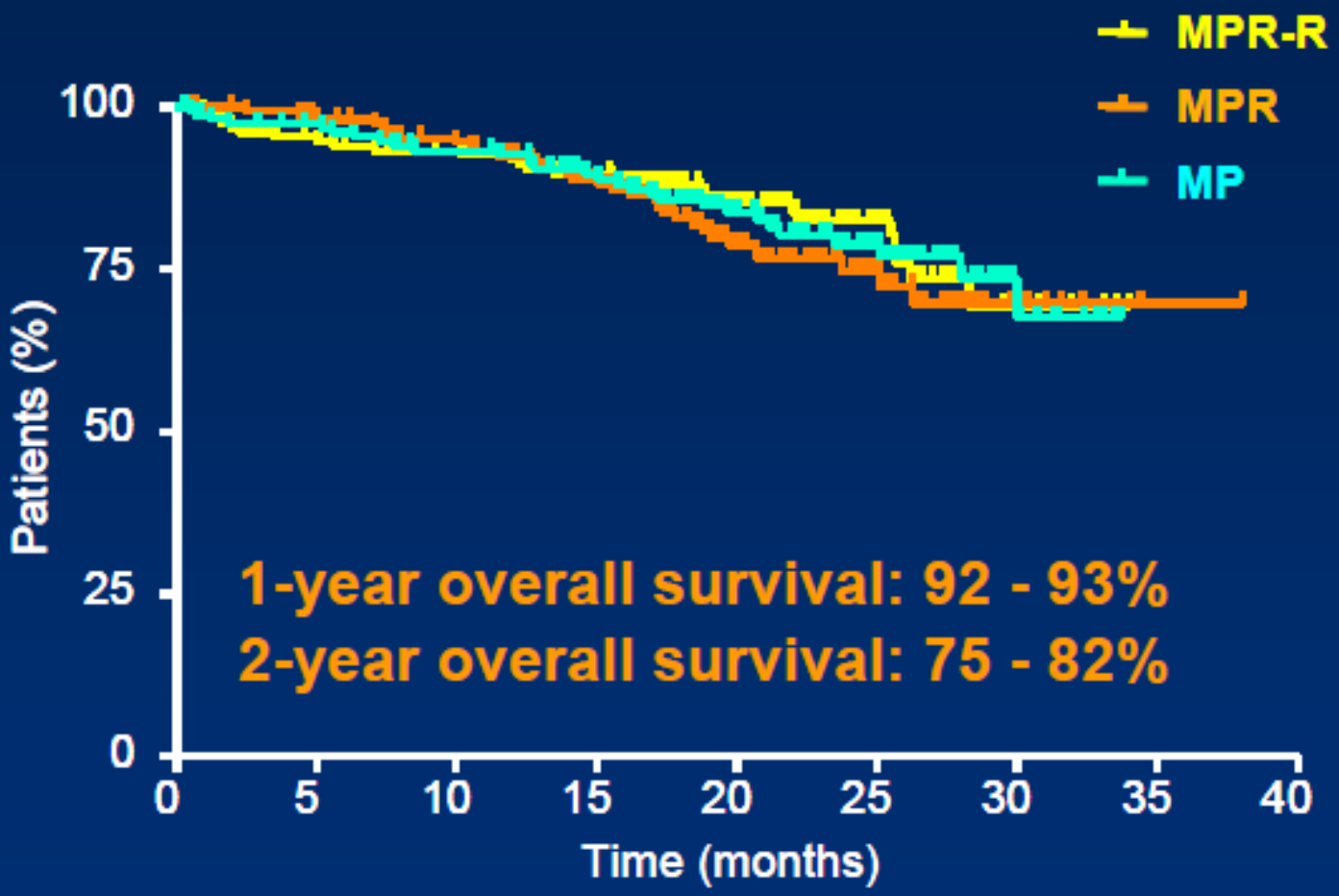
60% Reduced Risk of Progression



Median follow-up 25 months

*Analysis based on data up to May 2010

Overall Survival

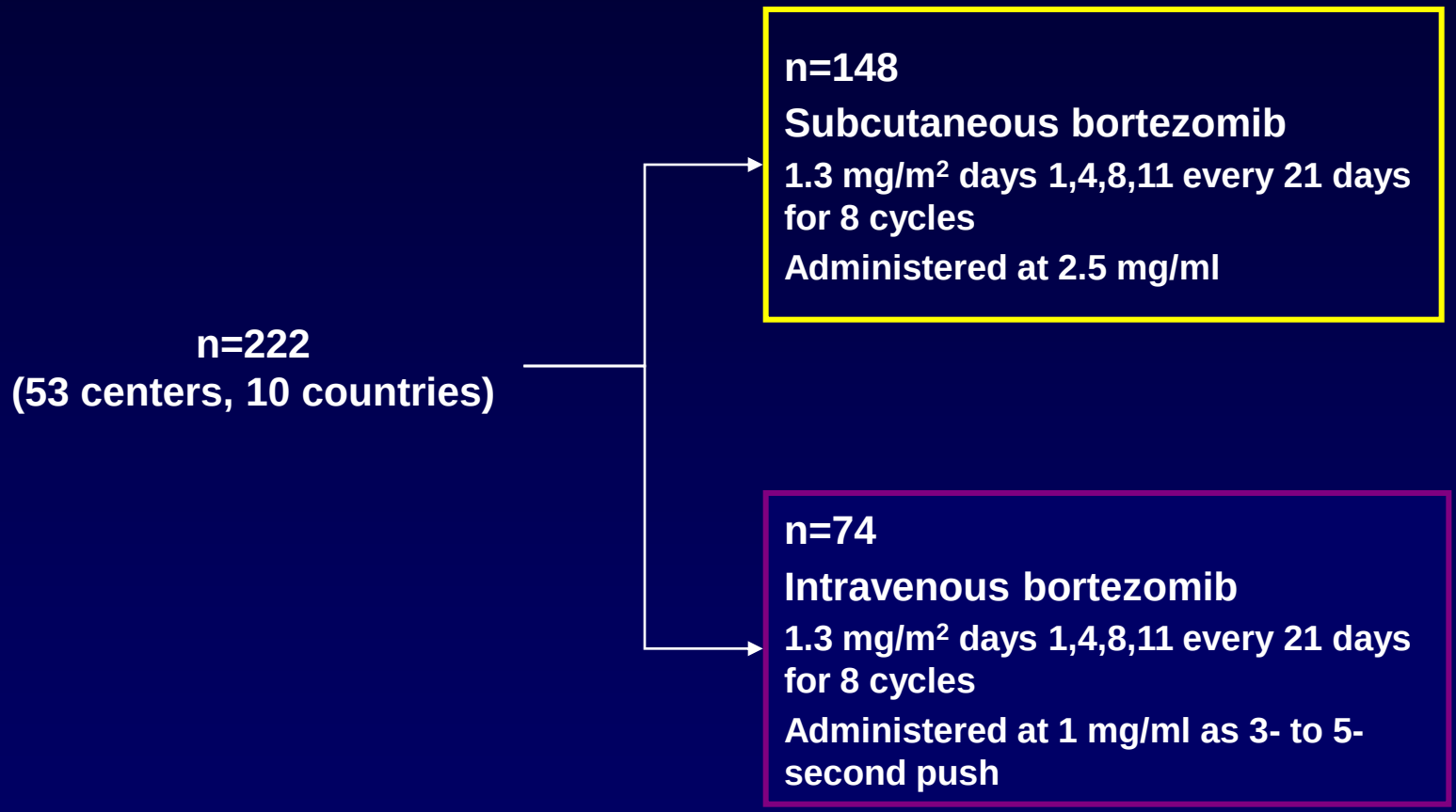


- Small number of events, median follow-up of 21 months

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

Philippe Moreau, Halyna V Pylypenko, Sebastian Grosicki, Evgeniy E Karamanesht, Xavier Leleu, Maria E Grishunina, Grigoriy B Rekhtman, Zvenyslava Masliak, Tadeusz Robak, Anna V Shubina, Jean-Paul Fermand, Martin Kropff, James Cavet, Sudha Parasuraman, Huaibao Feng, Donna M Skee, Helgi van de Velde, William M Deraedt, and Jean-Luc Harousseau

Phase III Trial Design

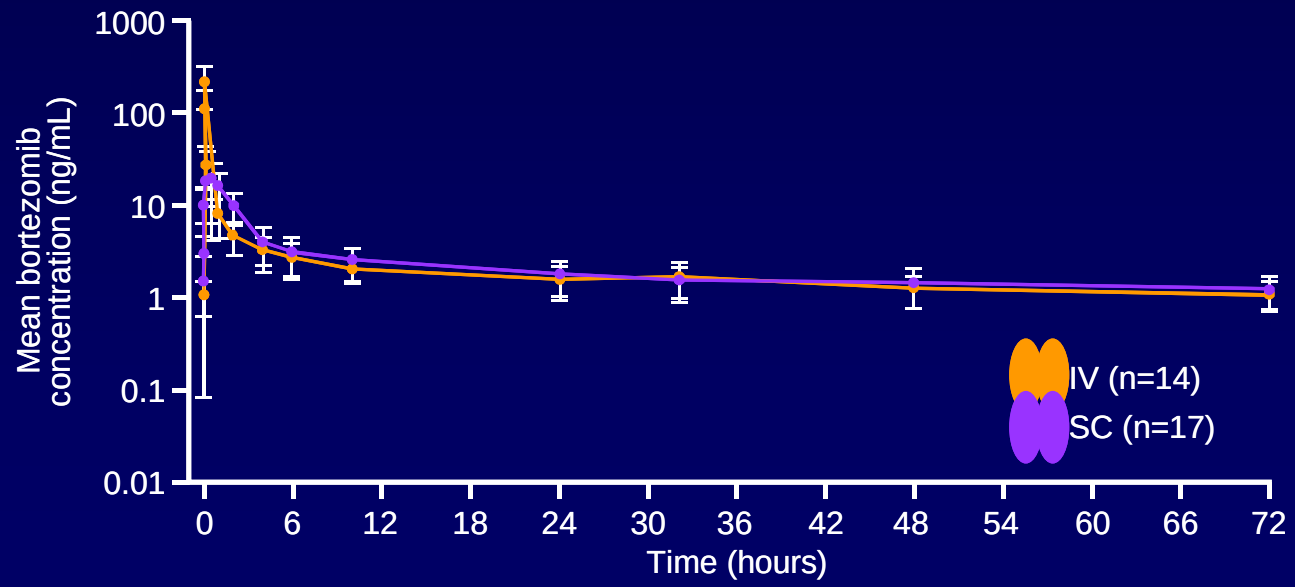


Cycles 1–4: bortezomib monotherapy
After 4 cycles: addition of dex 20 mg (days 1, 2, 4, 5, 8, 9 and 11, 12) if <PR

Moreau *et al.* ASH 2010

Pharmacokinetics

	Bortezomib IV (n=14)	Bortezomib SC (n=17)
T_{max}, hours, median (range)	0.08 (0.03–0.5)	2.00 (0.5–24)
E_{max},%, mean (SD)	69.3 (13.2)	63.7 (10.6)
AUE_{72}, %.h, mean (SD)	1383 (767)	1714 (617)



Moreau *et al.* ASH 2010

	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%

	Bortezomib IV	**Bortezomib SC**	
Any PN event	**53%**	**38%**	**0.04**
Grade ≥2	**41%**	**24%**	**0.01**
Grade ≥3	**16%**	**6%**	**0.03**

6% of patients had at least one SC injection site reaction reported as an AE

Moreau *et al.* ASH 2010

Others

- Myeloma stem cells
- Myeloma IX data
- Pomalidomide
- Carfilzomib
- CDK inhibitors

Summary

- High throughput co-culture model for investigating novel drugs and immunomodulatory agents
- Genomics for predicting bortezomib response & treatment emergent neuropathy
- Improvements in survival for high risk myeloma, but 17p- remains poor
- MPR-R: a new standard of care with lenalidomide maintenance extending PFS
- s.c bortezomib: same response, less toxicity

Acknowledgements

UKMF-Celgene Travel bursary

Barts and The London NHS
NHS Trust