Erasmus MC
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EMN

News in the therapy of multiple myeloma after ASH 2011

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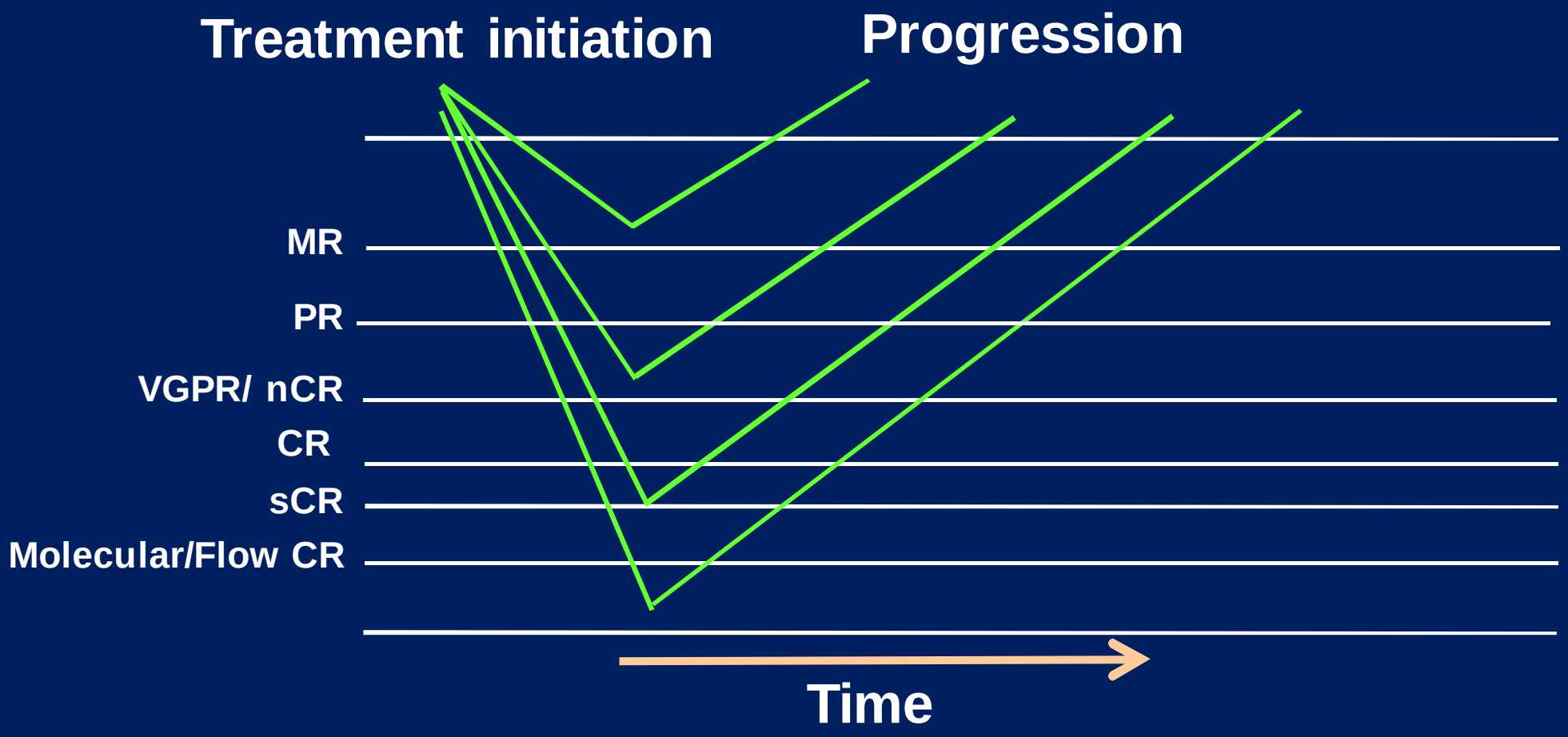
Which level of response is the goal upon treatment for relapse ?



Depth of response related to TTP ?

Adapted from: Niesvizky et al. Br J Haematol 2008; 143(1): 46–53; Harousseau et al. Blood 2009; 114(15): 3139-46 Chanan-Khan et al. J Clin Oncol 2010; 28(15): 2612-24

Importance of achieving high-quality response in the transplant setting

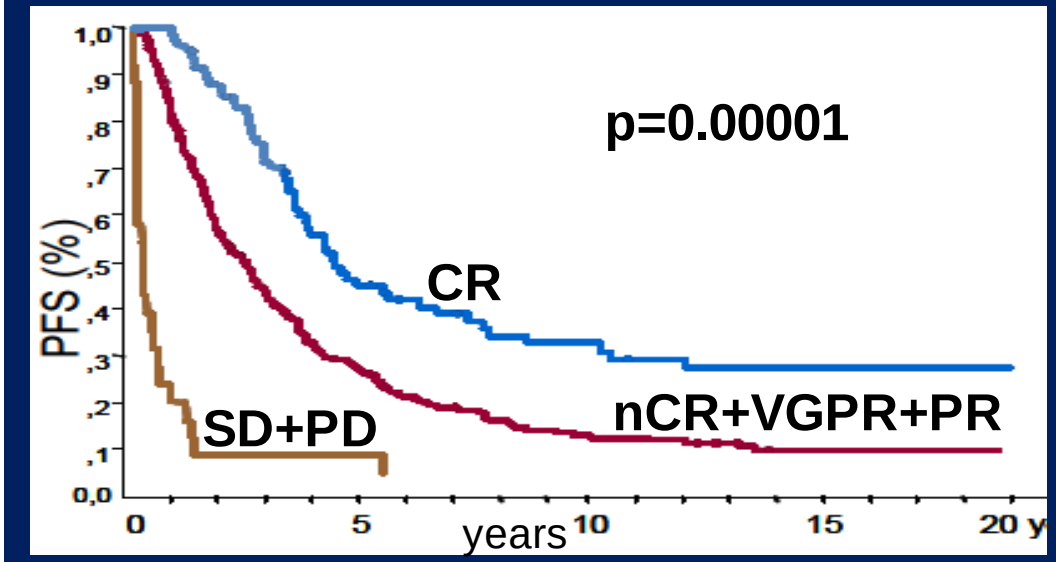
- A number of studies/analyses have demonstrated a link between high-quality response and outcome
  - Meta-analysis of 21 studies[1]
    - Significant association between maximal response and long-term outcome
  - IFM 2005-01 trial: VD vs VAD[2]
    - Achievement of VGPR after induction therapy a significant prognostic factor for PFS[2]
  - MRC Myeloma IX trial: CTD vs CVAD[3]
    - Achievement of CR associated with improved PFS
  - GIMEMA trial: VTD vs TD[4]
    - Achievement of CR/nCR significant prognostic factor for PFS

1. van de Velde et al. Haematologica 2007;92:1399–406
2. Moreau et al. Blood 2011;117(11):3041-3044
3. Morgan et al. Haematologica 2011 Epub, 4 November
4. Cavo et al. Lancet 2010;376:2075-85

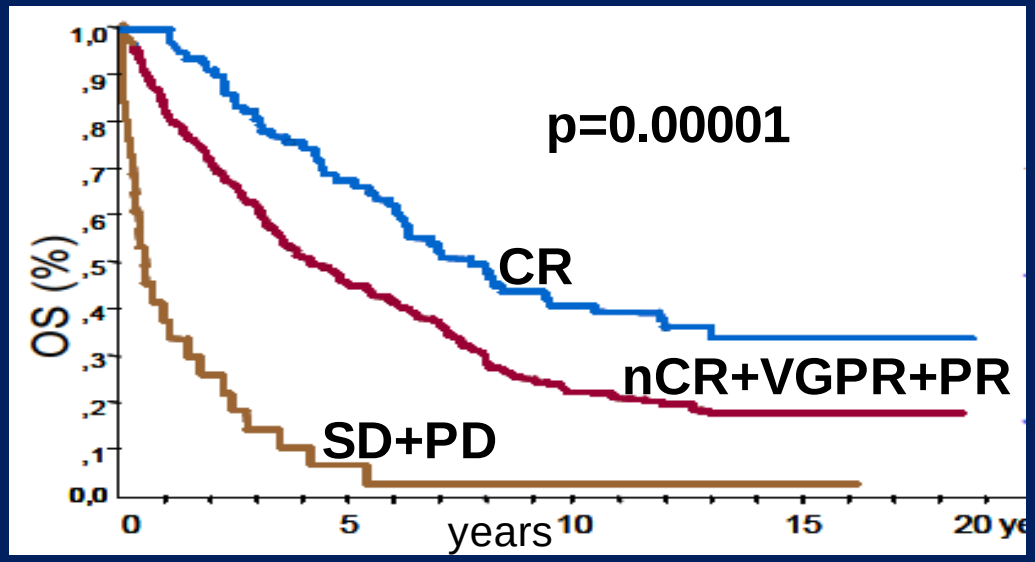
Importance of achieving high-quality response in the transplant setting

Prognostic impact of CR vs nCR/VGPR/PR vs SD/PD after high dose therapy plus ASCT (n=344)

PFS

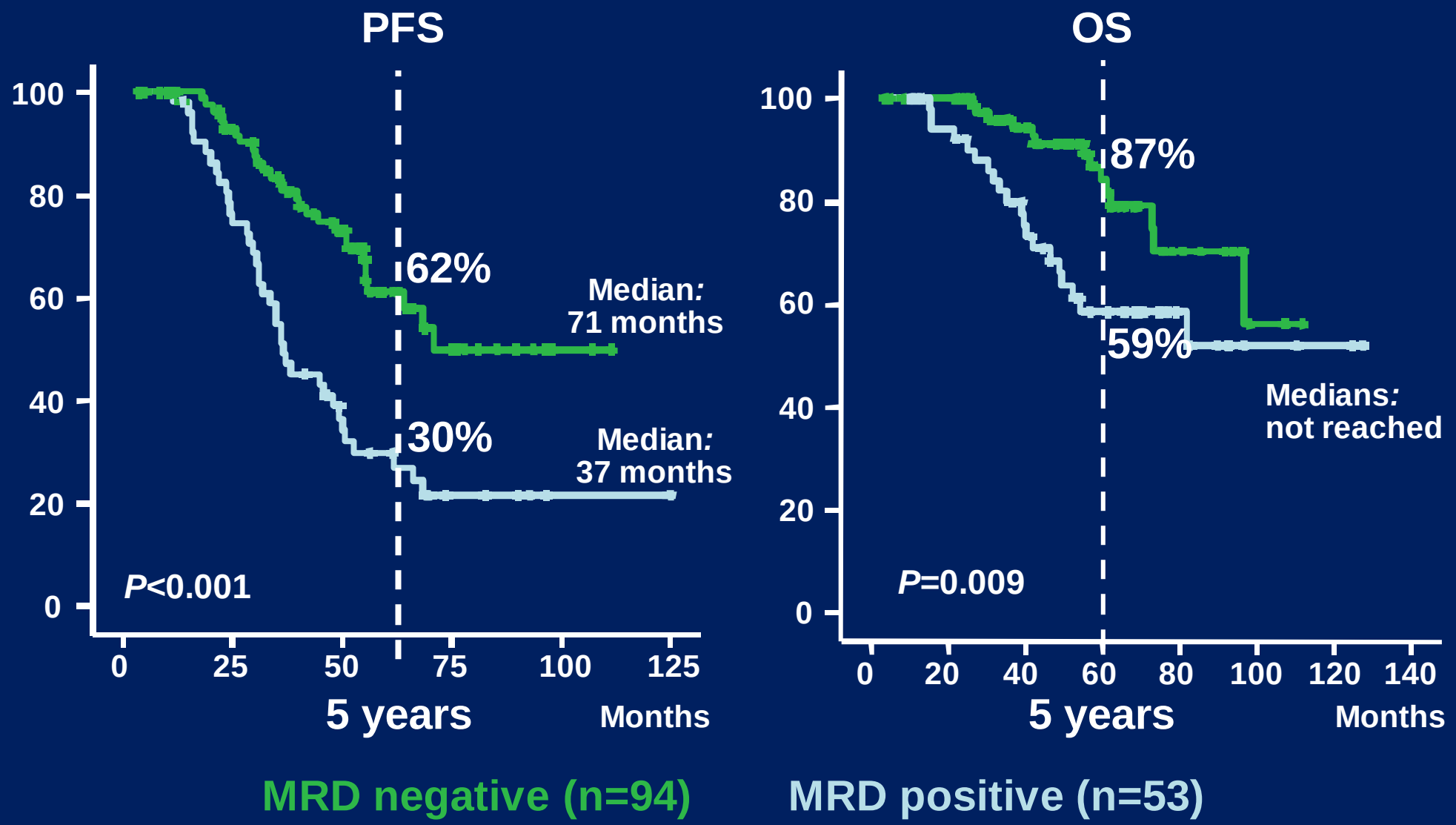


OS



Martinez-Lopez et al. Blood 2011;118(3):529-534

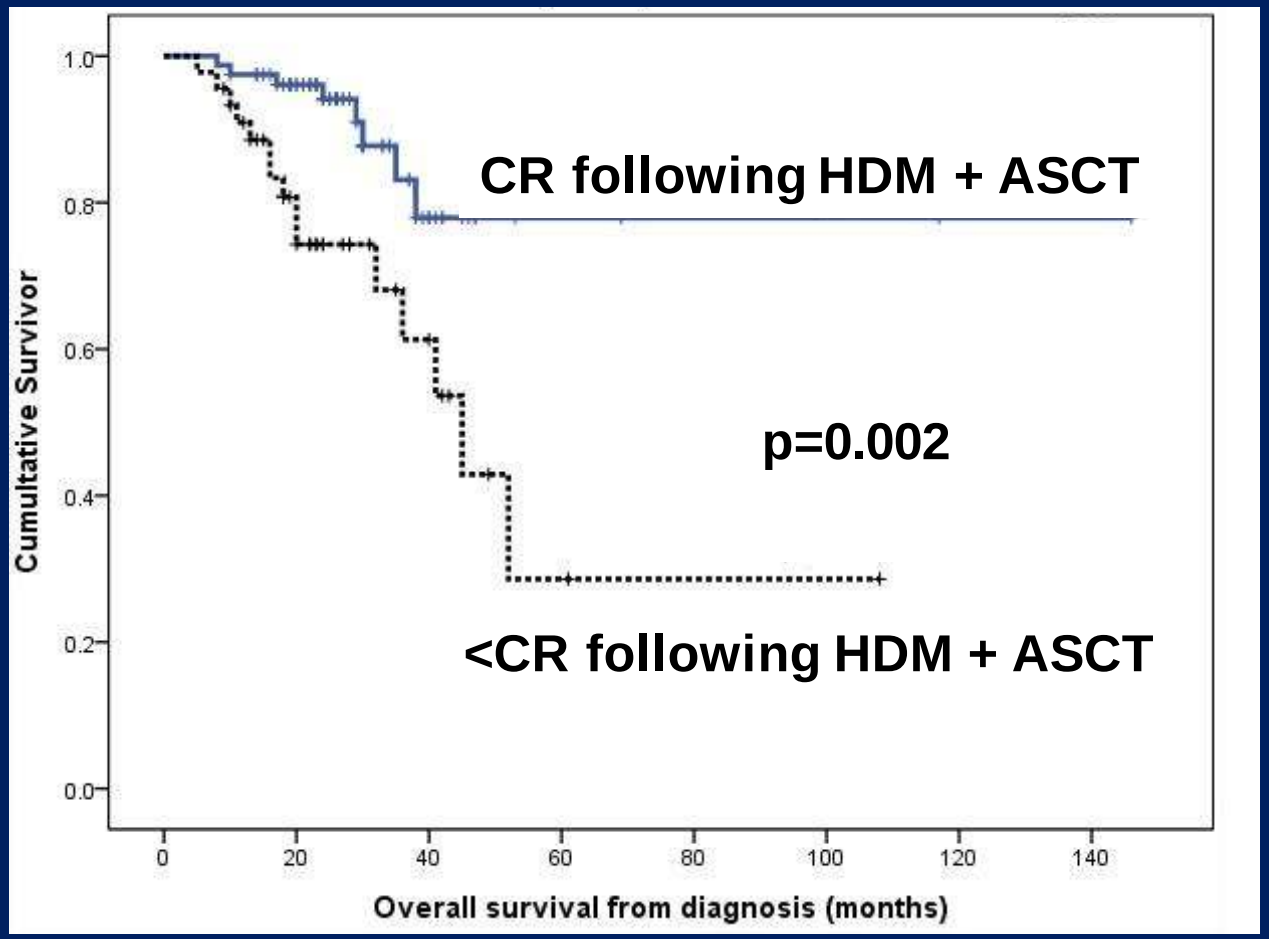
Impact of post-ASCT MRD detected by flow cytometry on clinical outcomes



Paiva et al. Blood 2008;112(10):4017–4023

Importance of achieving CR post-transplant

Retrospective analysis (n=126)

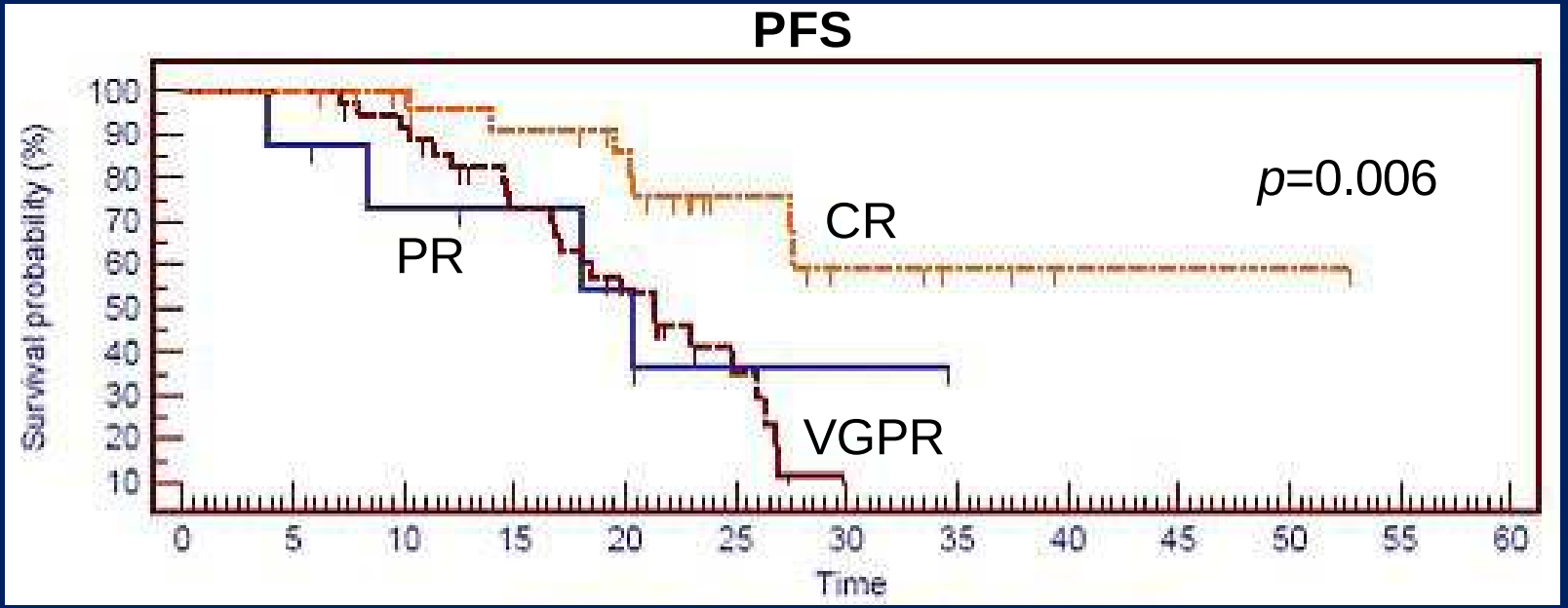


Achievement of CR post-ASCT is the only important prognostic regardless of response following induction

Shin et al. ASH 2011 (Abstract 2018), poster presentation

CR as major endpoint after consolidation

- **Prospective single center study**
  - **Patients (n=76) receiving consolidation if: 1) ≥ PR after HDM, 2) no grade ≥ 2 PN**
  - **Treatment: vTD 61%, lenalidomide 23%, Len/dex 13%, VRD 3%**
- **Results**
  - **Median follow up 20 months**



- **Patients with VGPR after HDM who upgrade response to CR after consolidation have longer PFS than who remain in VGPR (28 vs 20 mos, p=0.032)**

Hebraud et al. ASH 2011 (Abstract 1858), poster presentation

Importance of achieving high-quality response in the non-transplant setting

- **Link between quality of response and outcome has also been shown in the elderly population**
  - **CR correlates with long-term PFS and OS in elderly patients treated with novel agents[1]**
  - **Achieving an immunophenotypic response translates into superior PFS and TTP compared with conventional CR or sCR[2]**

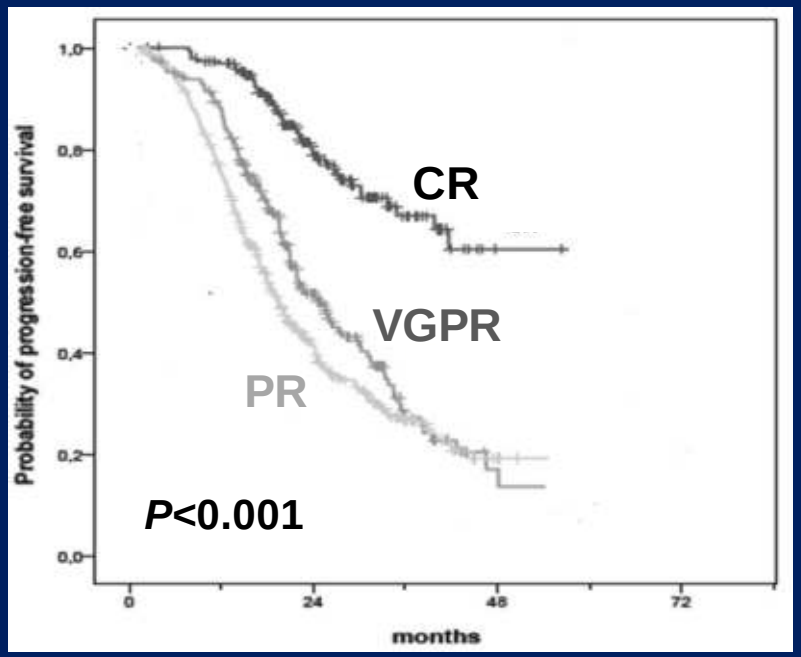
1. Gay et al. Blood 2011; 117(11): 3025-3031
2. Paiva et al. J Clin Oncol. 2011;29(12):1627-1633

CR correlates with long-term PFS and OS in elderly patients treated with novel agents

- Retrospective analysis:
  - 3 randomized trials of GIMEMA and HOVON groups (n=1175)
- First-line treatment

MP (n=332), MPT (n=332), VMP (n=257), VMPT-VT (n=254)

PFS



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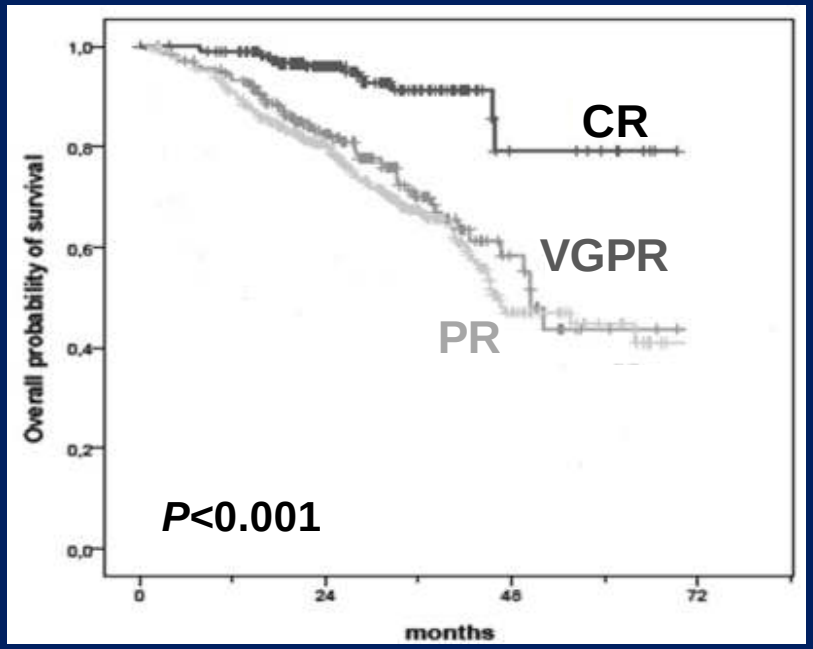
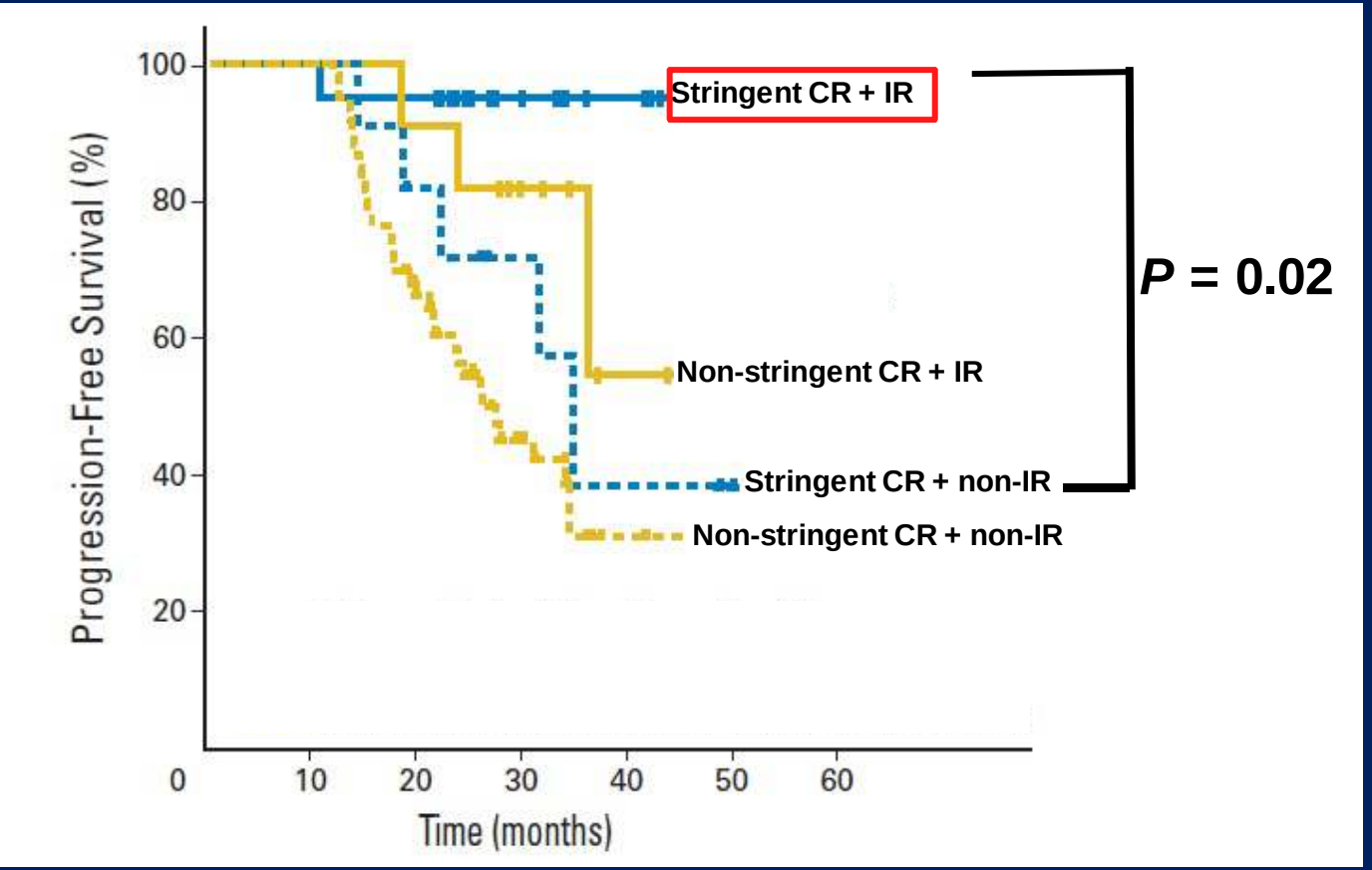


Gay et al. Blood 2011; 117(11): 3025-3031

Impact of achieving immunophenotypic response on long-term outcome in elderly patients

- Analysis of GEM2005>65y trial: VMP-VT/VP vs VTP-VT/VP in front-line
  - Patients (>65 years) with ≥PR after 6 cycles of VMP or VTP (n=102)



Longest PFS for patients in stringent CR plus IR

IR, immunophenotypic response

Paiva et al. J Clin Oncol. 2011;29(12):1627-1633

Which level of response is necessary?

- **Importance of MRD evaluation by multiparameter flow cytometry (MFC)[1]**
  - **MRD status by MFC at day 100 post-ASCT most important independent prognostic factor for PFS**
- **Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in MM[2]**
  - **Achieving an immunophenotypic response translates into superior PFS and TTP compared with conventional CR or sCR**

1. *Paiva et al. Blood 2008;112(10):4017–4023*
2. *Paiva et al. J Clin Oncol. 2011*;29(12):1627-1633

Prognostic implications of PET/CT-defined CR

- **18 F-FDG PET/CT: technique to detect the presence of active bone lesions and/or bone marrow involvement with high sensitivity and specificity**

- **Patients (n=192) with newly diagnosed MM undergoing ASCT**
- **Results**
  - **PET-CR (PET/CT negativity) after ASCT conferred superior PFS and OS**

	PET-CR	No PET-CR	p
4-year PFS	66%	45%	0.02
4-year OS	89%	65%	0.02

Zamagni et al. ASH 2011 (Abstract 826), oral presentation

Prognostic implications of PET/CT-defined CR

- Relationship between conventional definitions and PET-CT

	PET-CR	No PET-CR	p
4-year PFS in patients with CR according to conventional criteria	61%	30%	0.02
Mean time to relapse/progression in pts with with conventionally-defined relapse or progression	27.6 months	18 months	0.05

- Conclusions
  - PET-defined CR is an independent prognostic factor
  - PET/CT contributed to a more careful definition of CR

Zamagni et al. ASH 2011 (Abstract 826), oral presentation

Should CR be a treatment endpoint for all patients?

- There are myeloma patients who achieve CR but relapse early on ('rapid responders - early relapsing') †
- In most cases, MM is preceded by MGUS and some cases revert to an 'MGUS profile' after treatment ‡
- There are patients with 'non-responding, non-progressive' disease ¥

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† *Similar to some aggressive NHL subtypes; these MM patients may benefit from intensive-sequential therapy*

‡ *Monoclonal B-cell lymphocytosis in 5% of adults >60 years (Rawström NEJM 2008, 359:575)*

¥ *Avoid over-treatment*

San Miguel & Mateos. Haematologica 2011;96(9):1246-1248

Prognostic markers for the prediction of early relapse in patients with CR after ASCT

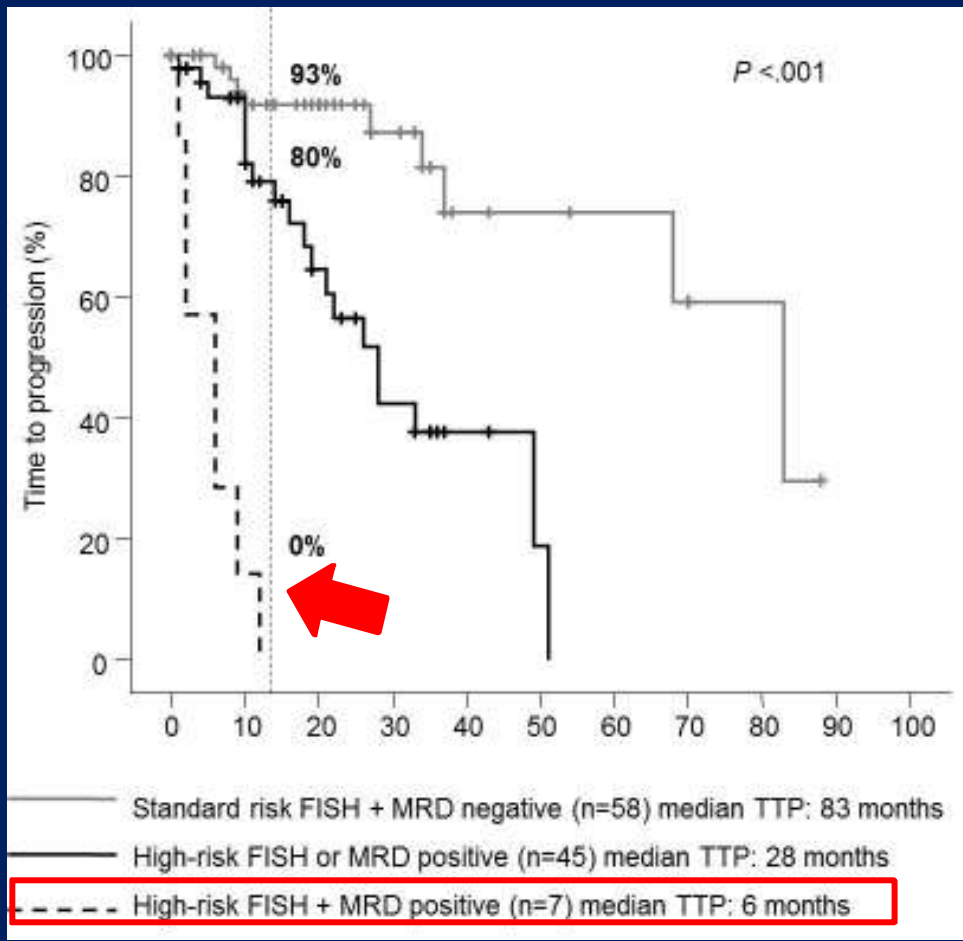
- **Patients (n=241) in CR in two GEM/PETHEMA trials**
  - **GEM2000: VBMCP/VBAD (n=140)**
  - **GEM2005<65y: Thal/dex vs Bortezomib/thal/dex vs VBMCP/VBAD + bortezomib (n=101)**

- **Establishing a predictive index to predict early relapse in patients with CR based on**
  - **Baseline evaluation of cytogenetic abnormalities**
  - **Response assessment by MRD after HDT/ASCT**

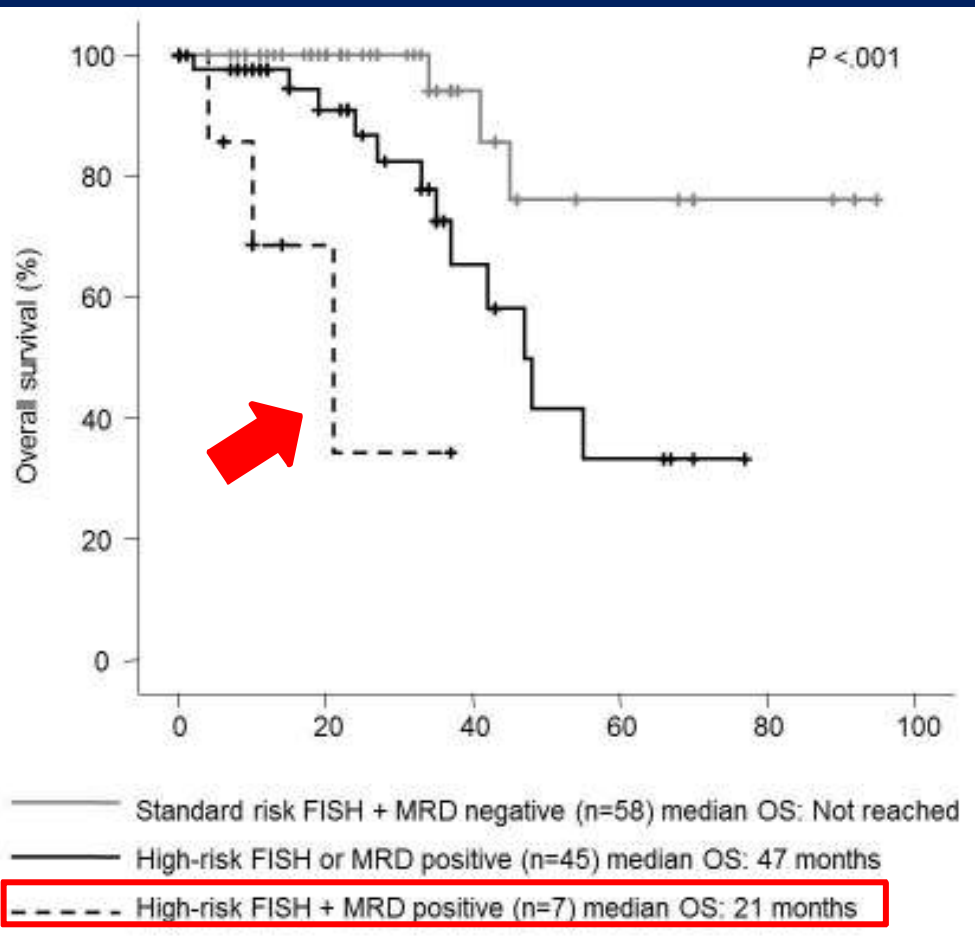
Paiva et al. ASH 2011 (Abstract 630), oral presentation
Paiva et al. Blood 2011, Nov 29 [Epub]

Prognostic markers for the prediction of early relapse in patients with CR after ASCT

TTP



OS



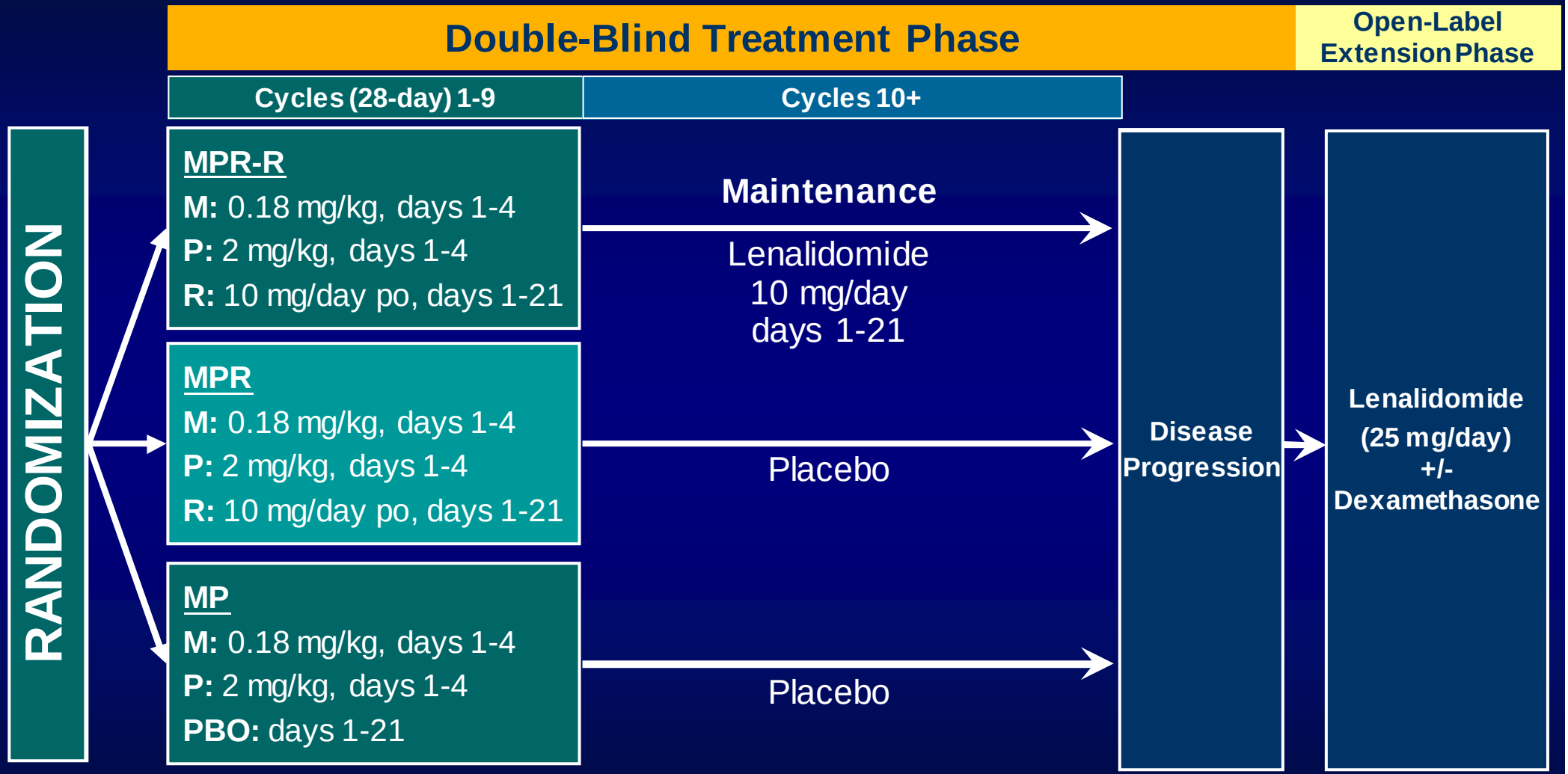
Paiva et al. ASH 2011 (Abstract 630), oral presentation
Paiva et al. Blood 2011, Nov 29 [Epub]

Open questions

- What are recommendations for routine practice regarding depth of response?
- Should response criteria be refined?
- How long to treat to achieve best response?
- Best response not feasible/needed in all patients
  - How to identify these?
- PFS versus OS

Review of new data in the treatment of patients not eligible for transplantation
1. Imids

MM-015: Study Design



- Stratified by age (≤ 75 vs > 75 years) and stage (ISS I/II vs III)
- Primary comparison: MPR-R vs MP

ISS, International Staging System; MP, melphalan, prednisone; MPR, melphalan, prednisone, lenalidomide; MPR-R, melphalan, prednisone, lenalidomide with lenalidomide maintenance; NDMM, newly diagnosed multiple myeloma; PBO, placebo.

MM-015: Updated results for patients 65-75 years old

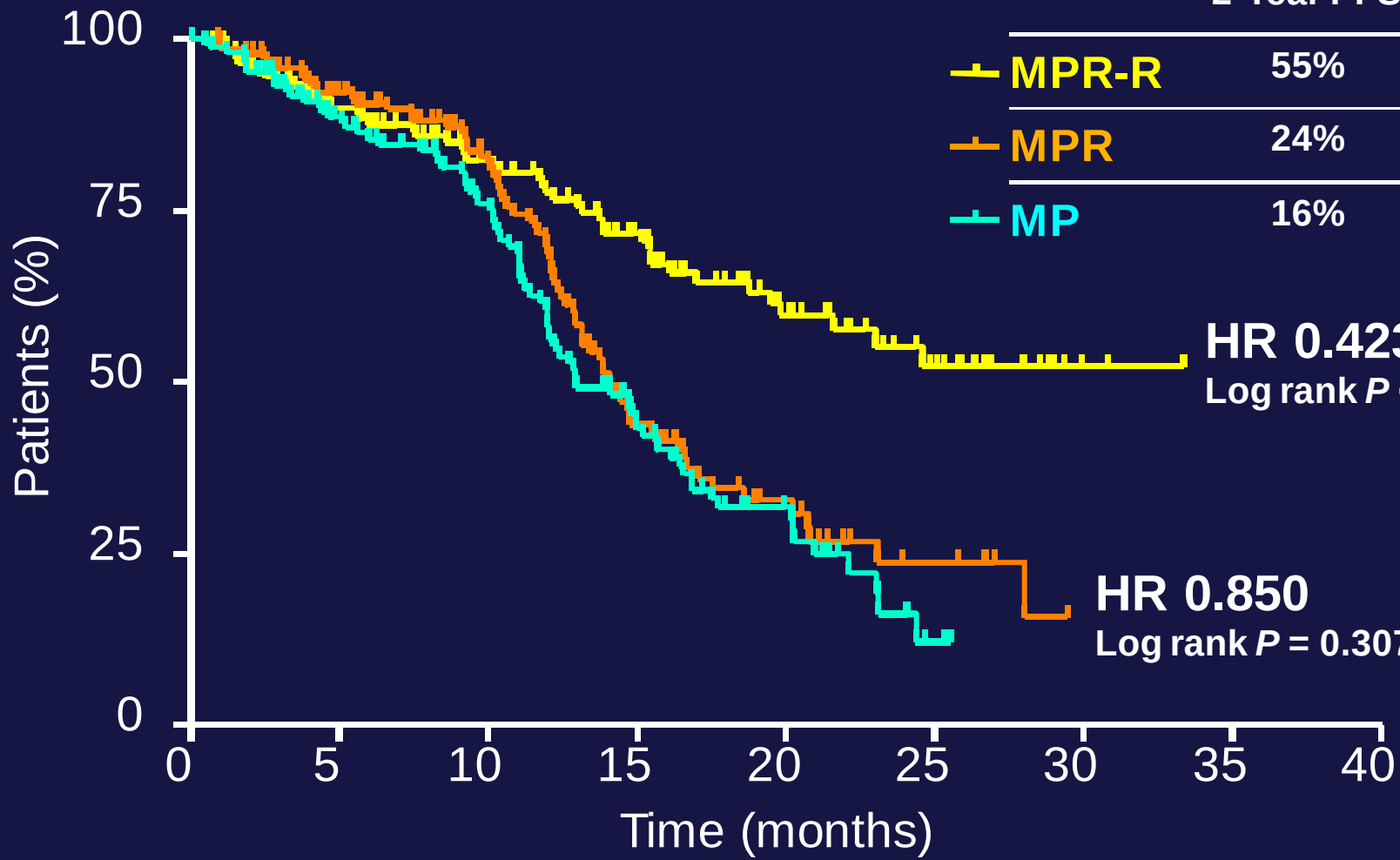
Median follow-up 30 months

	MPR-R	MPR	MP	p
Overall no. of pts	152	153	154	
No. of pts 65-75 years	116	116	116	
ORR	79.3%	73.3%	47.4%	
≥ VGPR	35.3%	35.3%	11.2%	
Median PFS	31 months*†	15 months†‡	12 months*‡	*†<0.001 ‡0.009

Palumbo et al. ASH 2011 (Abstract 475), oral presentation

Progression-Free Survival

All Patients

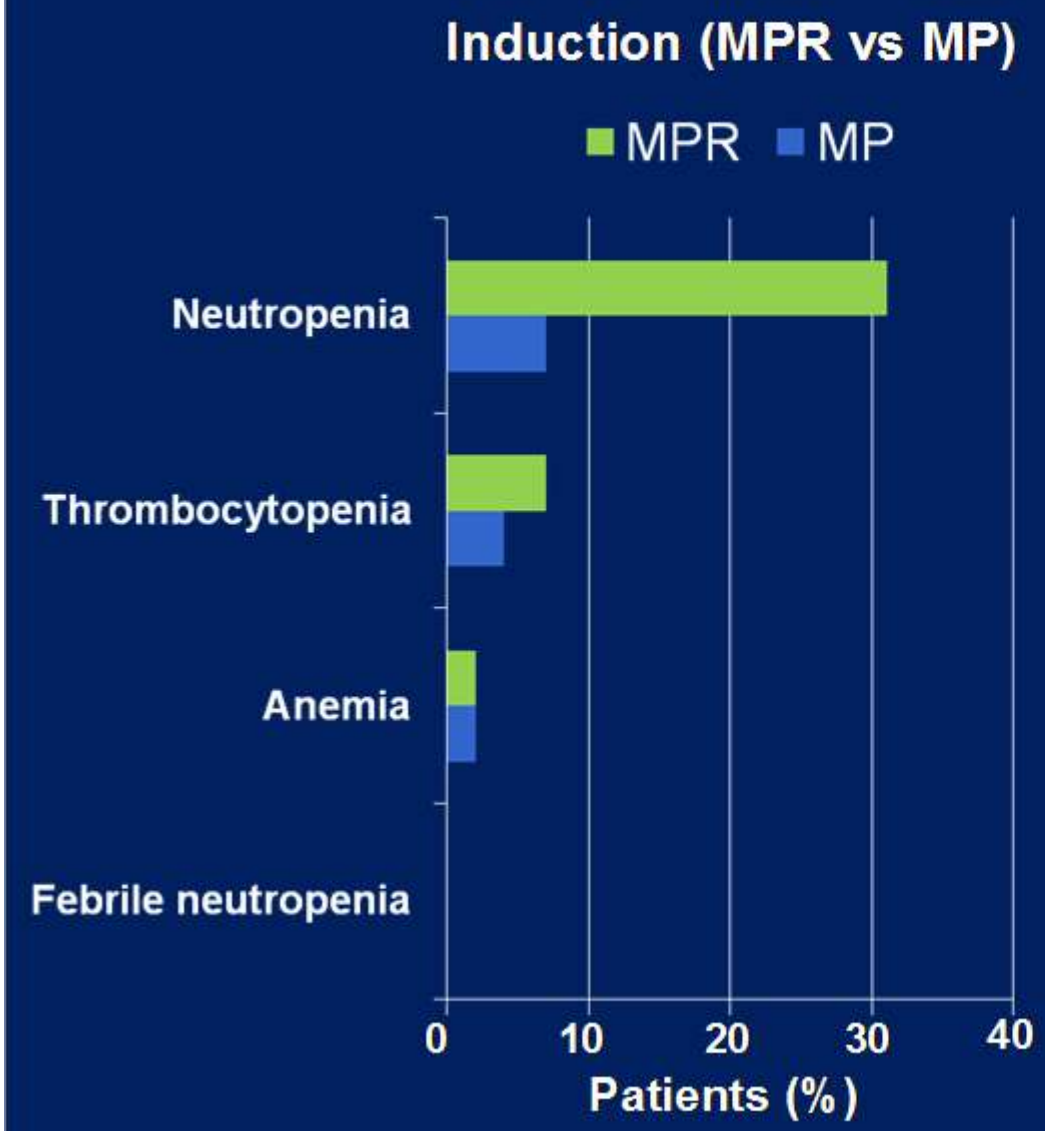


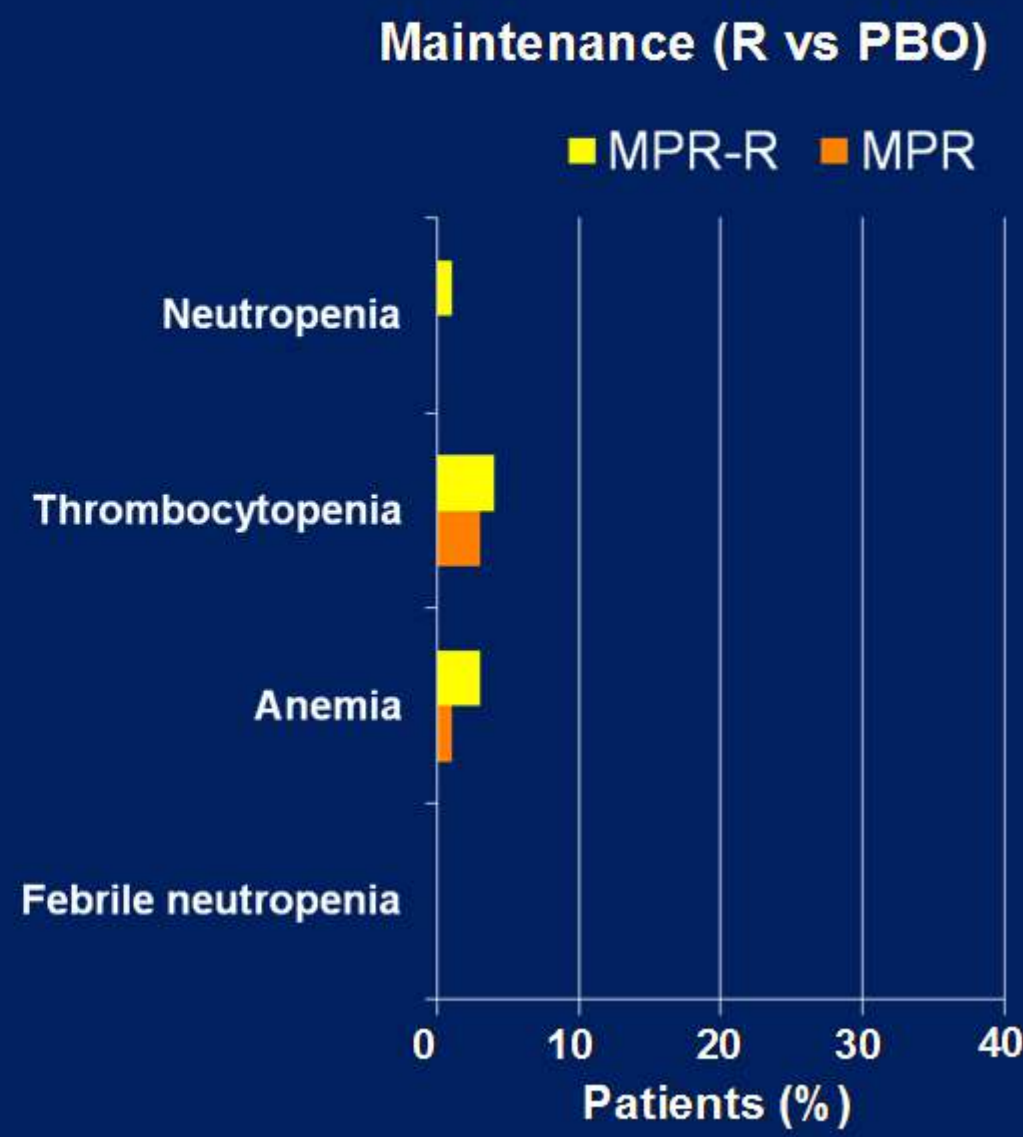
	2-Year PFS	Median PFS
MPR-R	55%	Not reached
MPR	24%	14.1 months
MP	16%	13.0 months

No. at Risk

MPR-R	152	115	89	66	35	17	2	–	–
MPR	153	120	90	36	17	7	–	–	–
MP	154	112	85	43	19	2	–	–	–

Grade 4 Hematologic Adverse Events
Safety Population, 65-75 years

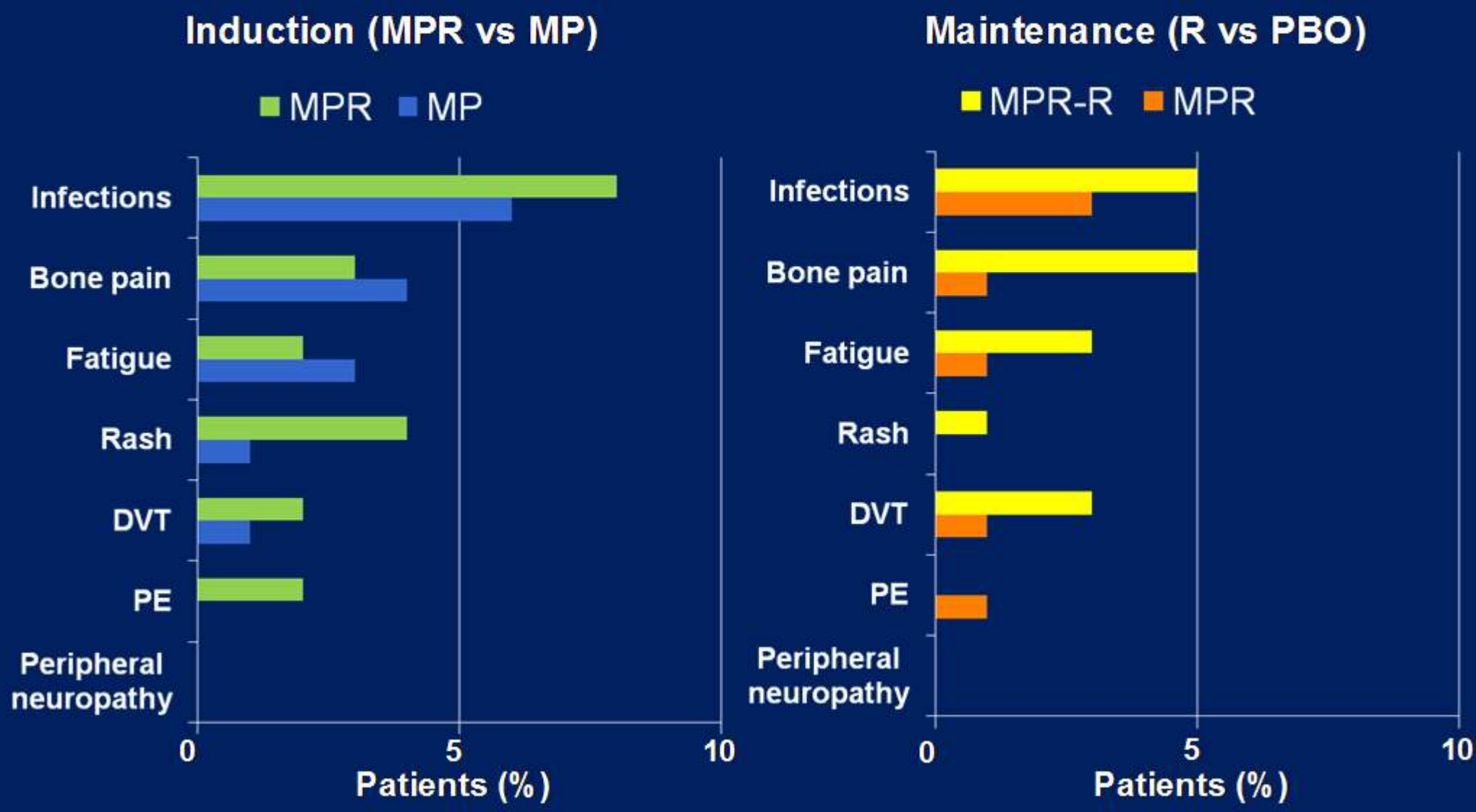




MP, melphalan, prednisone; MPR, melphalan, prednisone, lenalidomide; MPR-R, melphalan, prednisone, lenalidomide with lenalidomide maintenance; PBO, placebo.

Grade 3/4 Non-Hematologic Adverse Events

Safety Population, 65-75 years



DVT, deep vein thrombosis; MP, melphalan, prednisone; MPR, melphalan, prednisone, lenalidomide; MPR-R, melphalan, prednisone, lenalidomide with lenalidomide maintenance; PBO, placebo; PE, pulmonary embolism.

Discontinuation and Dose Intensity During Induction

	MPR[a]	MP
Discontinuation from induction < 9 cycles due to AE, %		
65-75 years of age	12	4
> 75 years of age	22	8
Cumulative dose intensity of melphalan, %		
65-75 years of age	83	83
> 75 years of age	50	72
Cumulative dose intensity of lenalidomide/placebo, %		
65-75 years of age	75	80
> 75 years of age	52	79

- MPR dose intensity for patients aged 65-75 years was acceptable with most patients remaining on therapy
- Dose intensity was reduced in patients aged > 75 years

[a] MPR includes MPR-R and MPR for the initial 9 cycles.
AE, adverse event; MP, melphalan, prednisone; MPR, melphalan, prednisone, lenalidomide.

Maintenance treatment in the non-transplant setting: thalidomide

	Median follow-up (months)	Median PFS (months)	Median OS (months)	Reference
MPT + T	38	21.8*	45.0	*Palumbo et al. Blood 2008; 112(8):3107-14*
vs				
MP		14.5	47.6	
MPT + T	39	13*	40*	*Wijermans et al. JCO 2010; 28(19):3160-6*
vs				
MP		9	31	
MPT + T	42	15	29	*Waage et al. Blood 2010; 116(9):1405-12*
vs				
MP		14	32	
CTDa/MP (CTD/CVAD) + T	5.8 years	Thal maintenance improves PFS* with no OS advantage		*Morgan et al. ASH 2011 (Abstract 993)*
vs				
CTDa/MP (CTD/CVAD)				
Thal-IFN	35	27.7*	52.6	*Ludwig et al. Haematologica 2010; 95(9):1548-54*
vs				
IFN†		13.2	51.4	

†Thal/Dex vs MP as induction

*significant difference between arms

Maintenance treatment in the non-transplant setting: lenalidomide and bortezomib

	Median follow-up (months)	Median PFS (months)	Median OS (months)	Reference
MPR + R	27 (PFS) 41 (OS)	31*	NR	*Palumbo et al. ASH 2011 (Abstract 475)*
vs				
MPR		14		
vs				
MP		13		
VMPT-VT	32	37*	NR	*Palumbo et al. ASH 2010 (Abstract 620)*
vs				
VMP		27		
VMP/VTP-VT	46	39	NR	*Mateos et al. ASH 2011 (Abstract 477)*
vs				
VMP/VTP-VP		32	60	

*significant difference between arms

Review of new data in the treatment of patients not eligible for transplantation update of VISTA

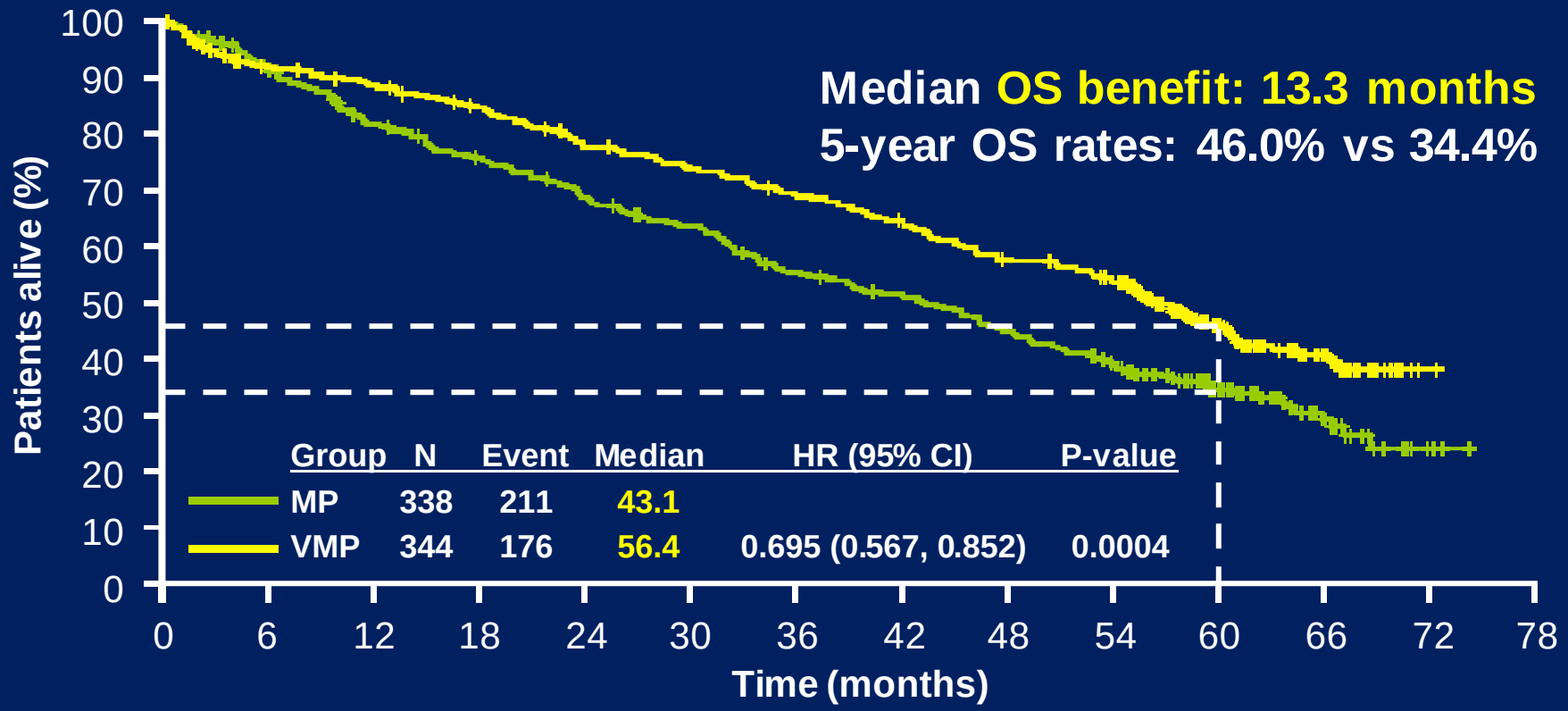
Background

- Patients (N=682) randomized to nine 6-week cycles of:
  - VMP (N=344):
    - Bortezomib 1.3 mg/m^2, days 1, 4, 8, 11, 22, 25, 29, and 32, cycles 1–4, then days 1, 8, 22, and 29, cycles 5–9
    - Melphalan 9 mg/m^2, days 1–4 of all cycles
    - Prednisone 60 mg/m^2, days 1–4 of all cycles
  - MP (N=338): melphalan and prednisone alone, as above
- Median age 71 years; 30% aged ≥75 years; 34% ISS stage III MM
- Per Protocol indicated that Patients followed at least every 12 weeks, for up to 4,5y following last-patient-in data, for survival and subsequent therapy use; median follow-up 60.1 months
  - Data cut-off: March 24, 2011; only 16 (5%) patients in each arm lost to follow-up
- Data on SPMs collected, by individual patient inquiries at all study sites during February 2011, from 655 (96%) patients

VISTA: Final updated OS analysis

31% reduced risk of death with VMP

Median follow-up 60.1 months



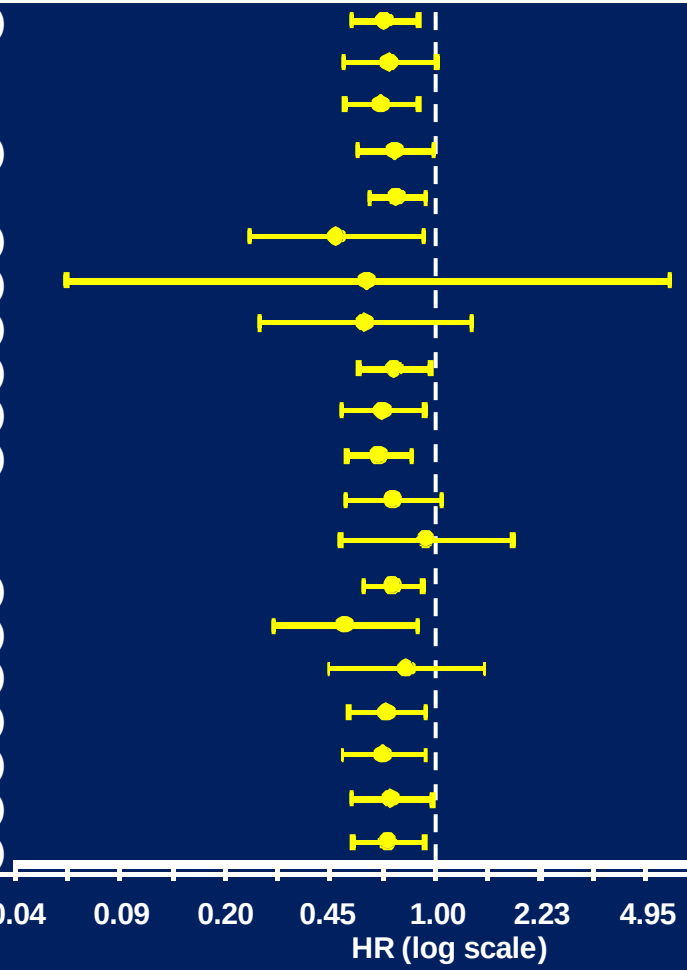
- **Meta-analysis of six phase 3 trials of thalidomide–MP (MPT) vs MP:[1]**
  - **Median OS: 39.3 vs 32.7 months (6.6-month benefit), HR 0.83, 17% reduced risk of death**

1. Fayers PM, et al. Blood 2011;118:1239–47.

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

OS in pre-specified subgroups

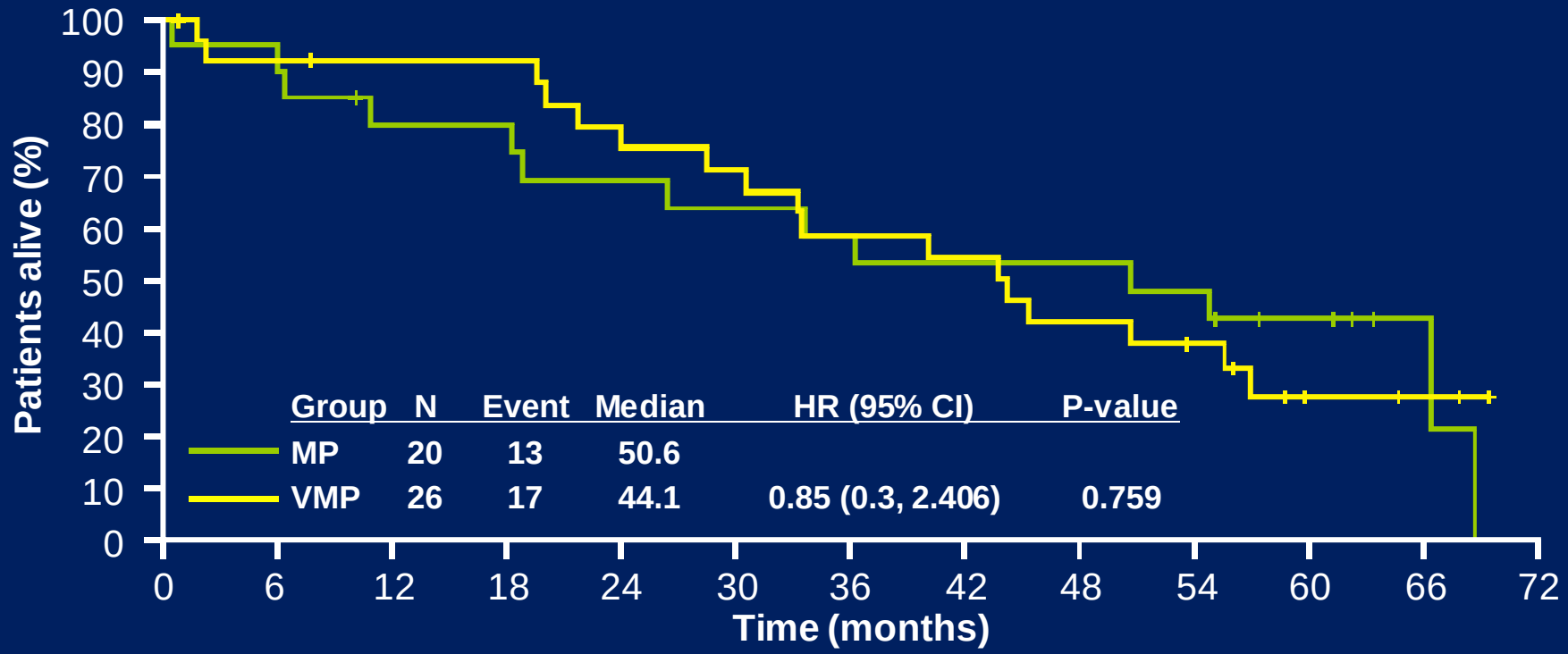
Group	Estimate	(95% CI)	MP Event/N	MP Median	VMP Event/N	VMP Median
Age (yrs): <75	0.68	(0.53, 0.88)	136/237	47.7	120/258	58.6
Age (yrs): ≥75	0.71	(0.5, 1.01)	75/101	32.9	67/115	50.7
Sex: Male	0.66	(0.5, 0.88)	109/166	36.7	101/188	55.4
Sex: Female	0.74	(0.55, 0.99)	102/172	46.4	86/185	60.6
Race: White	0.75	(0.6, 0.92)	179/295	45.0	165/333	56.9
Race: Asian	0.47	(0.24, 0.91)	28/36	17.2	19/33	50.8
Race: Other	0.6	(0.06, 5.95)	4/7	31.8	3/7	NA
B2-mgb (mg/dL): <2.5	0.59	(0.26, 1.32)	17/39	67.1	10/40	NA
B2-mgb (mg/dL): 2.5-5.5	0.73	(0.56, 0.96)	110/187	46.5	103/209	58.2
B2-mgb (mg/dL): >5.5	0.67	(0.49, 0.92)	84/112	30.5	74/124	42.1
Albumin (g/dL): <3.5	0.65	(0.51, 0.83)	148/209	34.8	127/222	50.8
Albumin (g/dL): ≥3.5	0.73	(0.5, 1.05)	62/128	59.4	58/149	NA
Region: N America	0.93	(0.48, 1.8)	17/30	46.4	19/32	55.9
Region: Europe	0.72	(0.58, 0.91)	161/265	45.0	147/302	56.9
Region: Other	0.5	(0.29, 0.87)	33/43	23.6	21/39	55.6
ISS stage: I	0.8	(0.44, 1.45)	25/64	NA	21/67	NA
ISS stage: II	0.69	(0.52, 0.92)	101/159	43.3	90/176	56.4
ISS stage: III	0.67	(0.49, 0.92)	85/115	30.5	76/130	42.1
Creat Clr: ≥60 mL/min	0.72	(0.53, 0.98)	90/154	52.7	88/175	56.2
CreatClr: < 60 mL/min	0.7	(0.53, 0.92)	121/184	36.7	99/198	56.8



- OS benefit with VMP seen across pre-specified patient subgroups, including:
  - Age ≥75 years – median 50.7 vs 32.9 months (HR 0.71)
  - ISS Stage III – median 42.1 vs 30.5 months (HR 0.67)
  - Creatinine clearance <60 mL/min – median 56.8 vs 36.7 months (HR 0.70)

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

OS in patients with high-risk cytogenetics

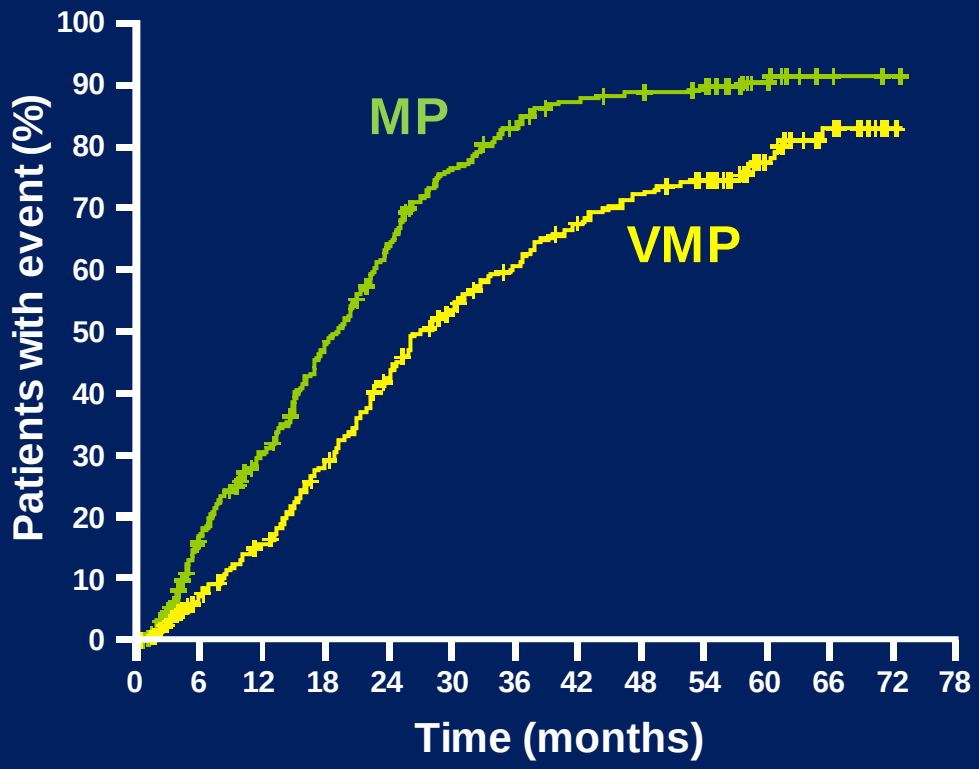


- Small subgroup (n=46; 26 VMP, 20 MP) with high-risk cytogenetics (= any of t(4;14), t(14;16), del(17p))
- No significant difference in OS between arms
  - Curves cross following median time to second-line therapy with VMP
  - Lower proportion of VMP vs MP patients with high-risk cytogenetics received subsequent bortezomib-based therapy (38% vs 60%)

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

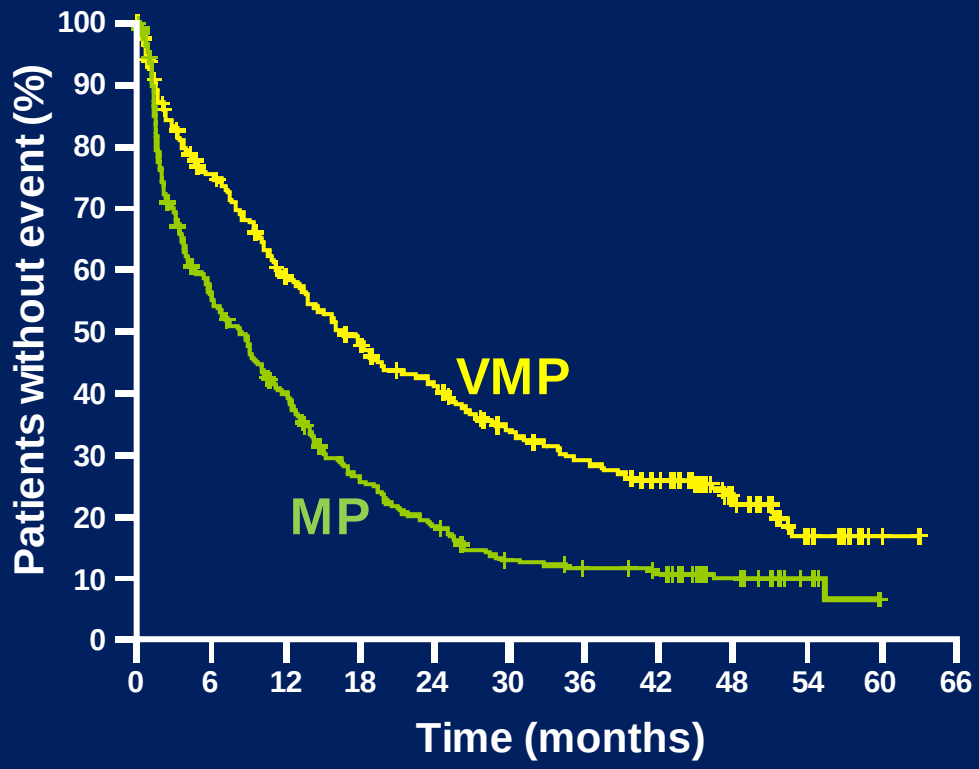
Time to next therapy / treatment-free interval

Time to next therapy (TTNT)



Median 27.0 vs 19.2 months
HR 0.557 (95% CI: 0.462, 0.671)
***P* < 0.0001**

Treatment-free interval (TFI)



Median 16.6 vs 8.3 months
HR 0.573 (95% CI: 0.476, 0.69)
***P* < 0.0001**

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

Subsequent therapies

Subsequent therapy, n (%)	VMP (n=344)	MP (n=338)
Any	215 (63)	246 (73)
Thalidomide	103 (30)	122 (36)
Lenalidomide	84 (24)	63 (19)
Bortezomib	77 (22)	145 (43)
Cyclophosphamide	95 (28)	78 (23)
Melphalan	79 (23)	72 (21)
Dexamethasone	140 (41)	165 (49)
Prednisone	69 (20)	61 (18)

- Use of subsequent therapies generally similar between arms
  - Lower proportion of VMP vs MP pts received subsequent bortezomib
  - Investigator-assessed response rates to subsequent bortezomib were 50% following VMP (i.e. bortezomib retreatment) and 58% following MP
  - Respective response rates to subsequent thalidomide were 46% and 55%, and to subsequent lenalidomide were 62% and 56%

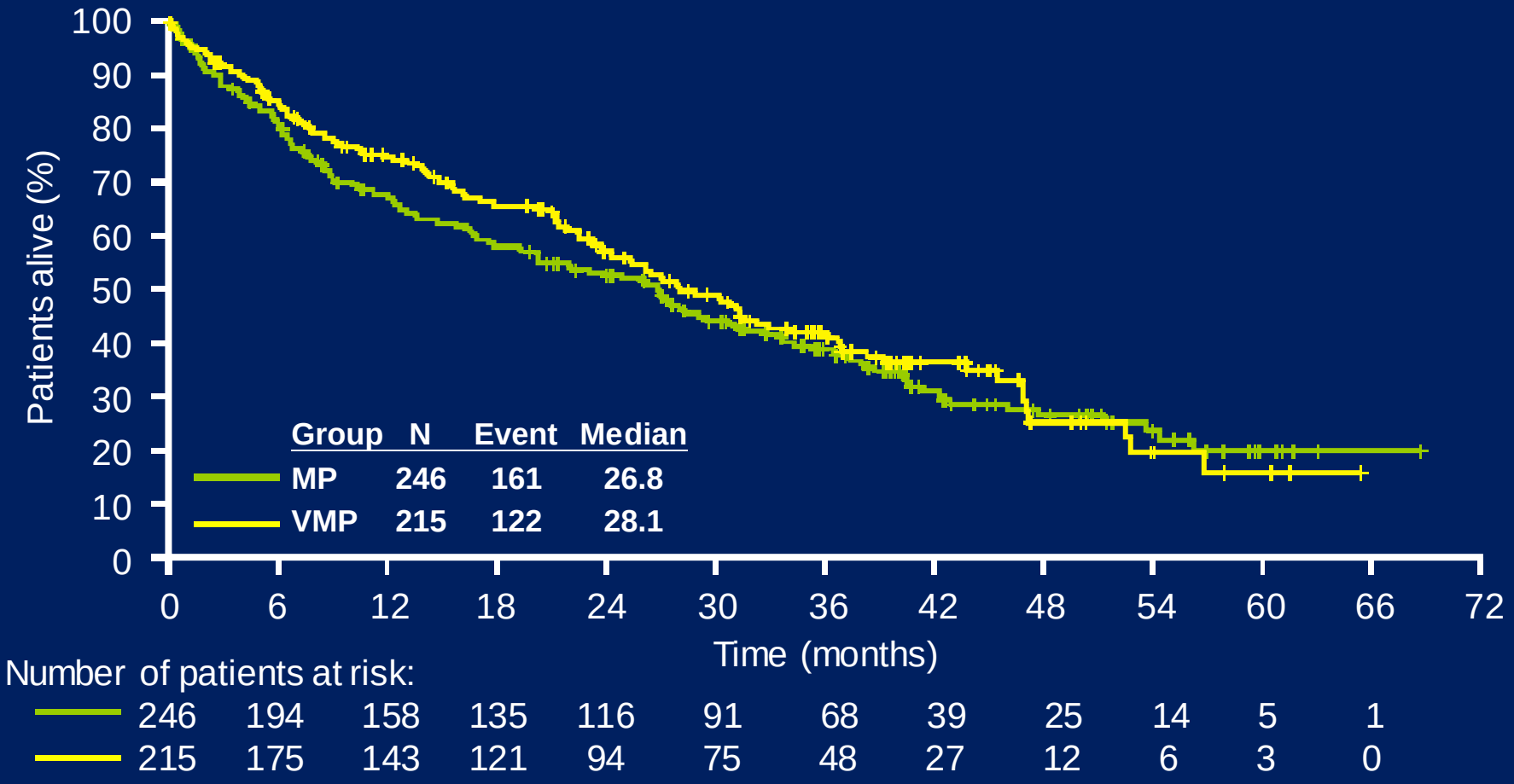
San Miguel et al. ASH 2011 (Abstract 476), oral presentation

Analyses of OS according to subsequent therapies

- **Does VMP induce more resistant relapses?**
- **Is there also an OS benefit in favour of VMP in relapsing patients?**
- **What about using MP upfront and reserving bortezomib for the time of relapse?**

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

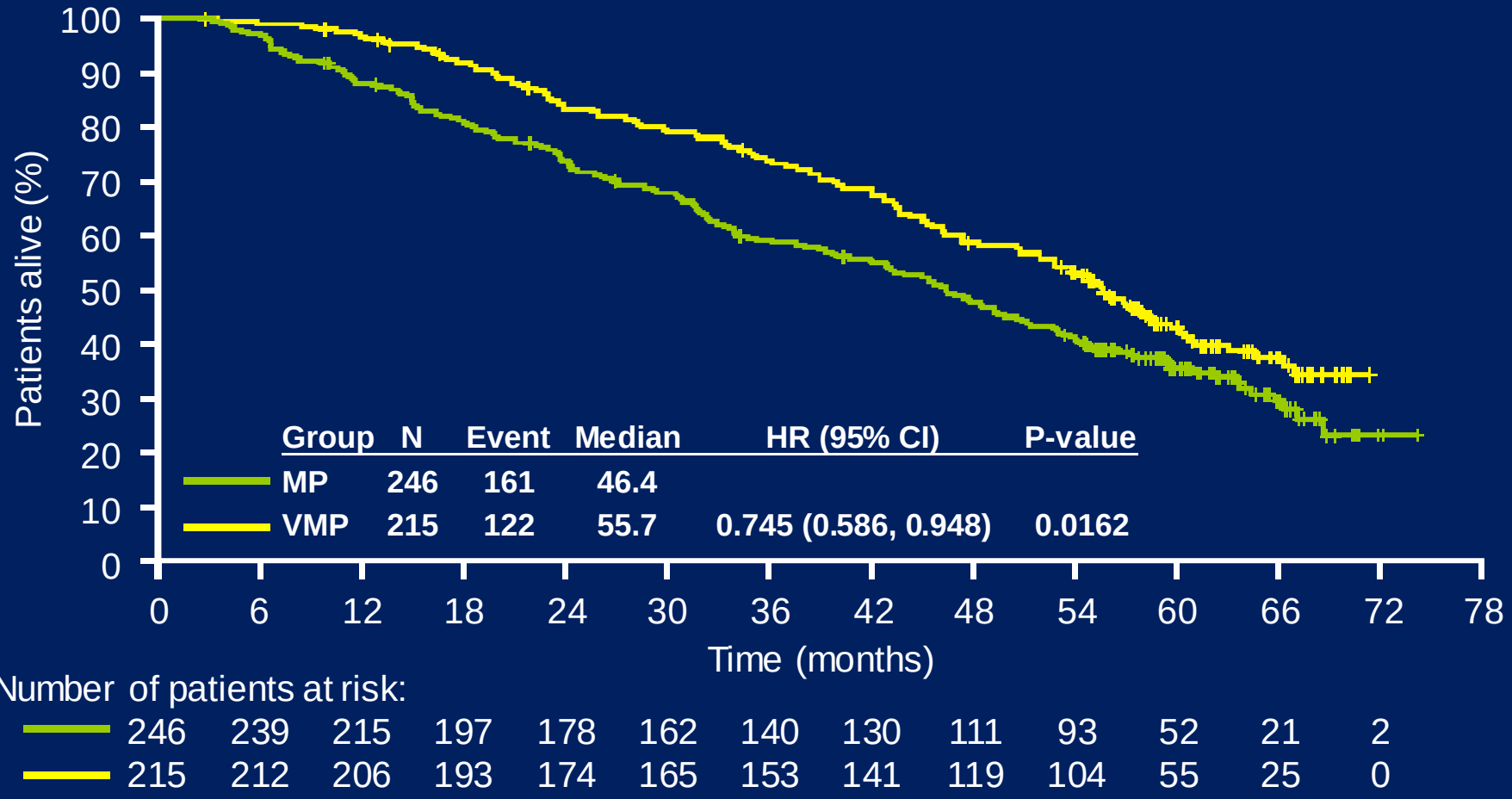
Survival from start of subsequent therapy similar following VMP and MP



- **VMP does not induce more resistant relapses**
- Analysis bias vs VMP due to exclusion of higher proportion of most sensitive patients (i.e. those still responding to therapy) and thus inclusion of poorer prognosis patients who relapsed more rapidly on VMP

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

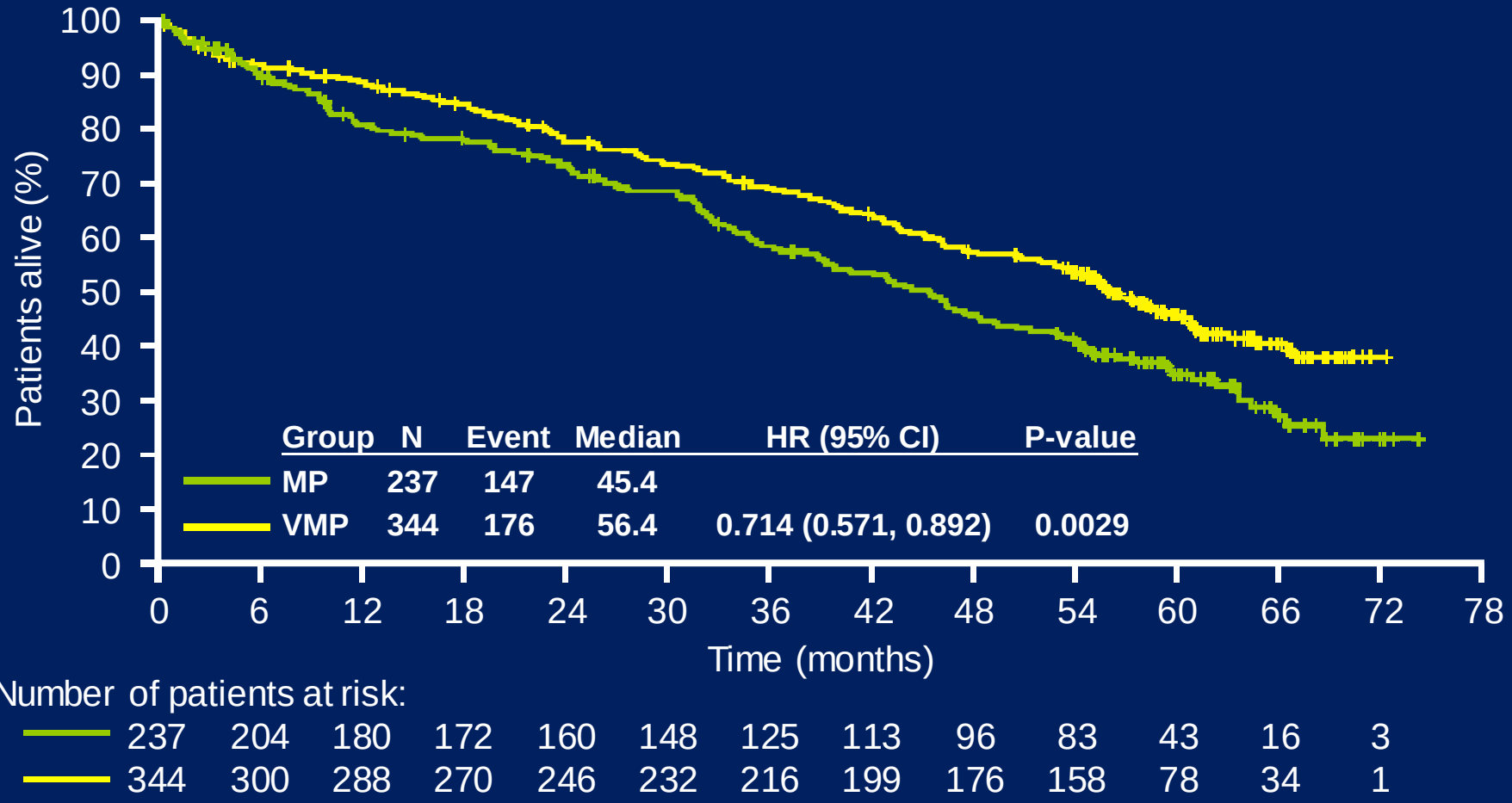
OS prolonged with VMP vs MP among all patients receiving subsequent therapies



- Bias against VMP due to omission of higher proportion of VMP vs MP patients who experienced most benefit from treatment; i.e. those who had not yet required subsequent therapy (35% vs 23%)

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

OS prolonged with VMP vs paradigm of first-line MP followed by salvage bortezomib



- Analysis includes all VMP patients, versus MP patients who have not received second-line therapy (due to not having relapsed, or due to death) plus those who received bortezomib salvage

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

SPMs: Incidence proportion

SPMs, n (%)	VMP (N=327)	MP (N=328)	RR (95% CI)
Hematologic SPMs	3 (1%)	3 (1%)	1.003 (0.204, 4.933)
AML	2 (1)	2 (1)	
B-cell lymphoma	0	1 (<1)	
MDS	1 (<1)	0	
Fatal hematologic SPMs	2 (1)	3 (1)	0.669 (0.113, 3.976)
Non-hematologic SPMs	16 (5%)	10 (3%)	1.605 (0.739, 3.484)
GI	5 (2)	4 (1)	
Renal/prostate	4 (1)	3 (1)	
Respiratory	2 (1)	0	
Skin	2 (1)	0	
Other	3 (1)	3 (1)	
Fatal non-hematologic SPMs	6 (2)	6 (2)	1.003 (0.327, 3.078)

Non-fatal SPMs: 1 MDS (VMP), 3 GI (VMP), 2 renal/prostate (each arm), 1 respiratory (VMP), 2 skin (VMP), 2 other (each arm)

No emerging safety signal for SPMs following VMP

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

SPMs: exposure-adjusted incidence rate

SPM incidence rate, n per 100-patient-years	VMP (N=327)	MP (N=328)	RR (95% CI)
Exposure, patient-years	1167	1004	
Hematologic SPMs	0.26	0.30	0.862 (0.174, 4.269)
Fatal	0.17	0.30	0.574 (0.096, 3.436)
Non-hematologic SPMs	1.40	1.00	1.389 (0.630, 3.061)
Fatal	0.52	0.60	0.859 (0.277, 2.664)
Overall rate	1.66	1.30	
Background rate, all cancers, general US population aged 65-74 years, 2004–2008[1]	1.92		

- No increased risk of SPMs with addition of bortezomib to MP
- Overall incidence rates in both arms consistent with background rate of all cancers in the general US population aged 65–74 years[1]

1. Howlader N, et al. SEER Cancer Statistics Review, 1975-2008. http://seer.cancer.gov/csr/1975_2008/browse_csr.php?section=2&page=sect_02_table.07.html

San Miguel et al. ASH 2011 (Abstract 476), oral presentation

Maintenance therapy with Bortezomib plus Thalidomide (VT) or Bortezomib plus Prednisone (VP) in elderly Myeloma patients included in the *GEM2005MAS65* spanish randomized trial

Mateos et al. ASH 2011 (Abstract 477), oral presentation

Efficacy: Response rate to maintenance therapy (n=178)

After a median of 20 months of maintenance therapy (1-36)

CR (IF-) increased from 24% (after induction) up to 42% (maintenance)

	Pre-maintenance	VT (n: 91)	VP (n:87)
IF-CR	24 %	**46 %**	**39 %**
IF+CR, %	10 %	10 %	11 %
PR, %	47 %	39 %	47 %
MR, %	8 %	3 %	1 %
SD, %	10 %	1 %	1 %

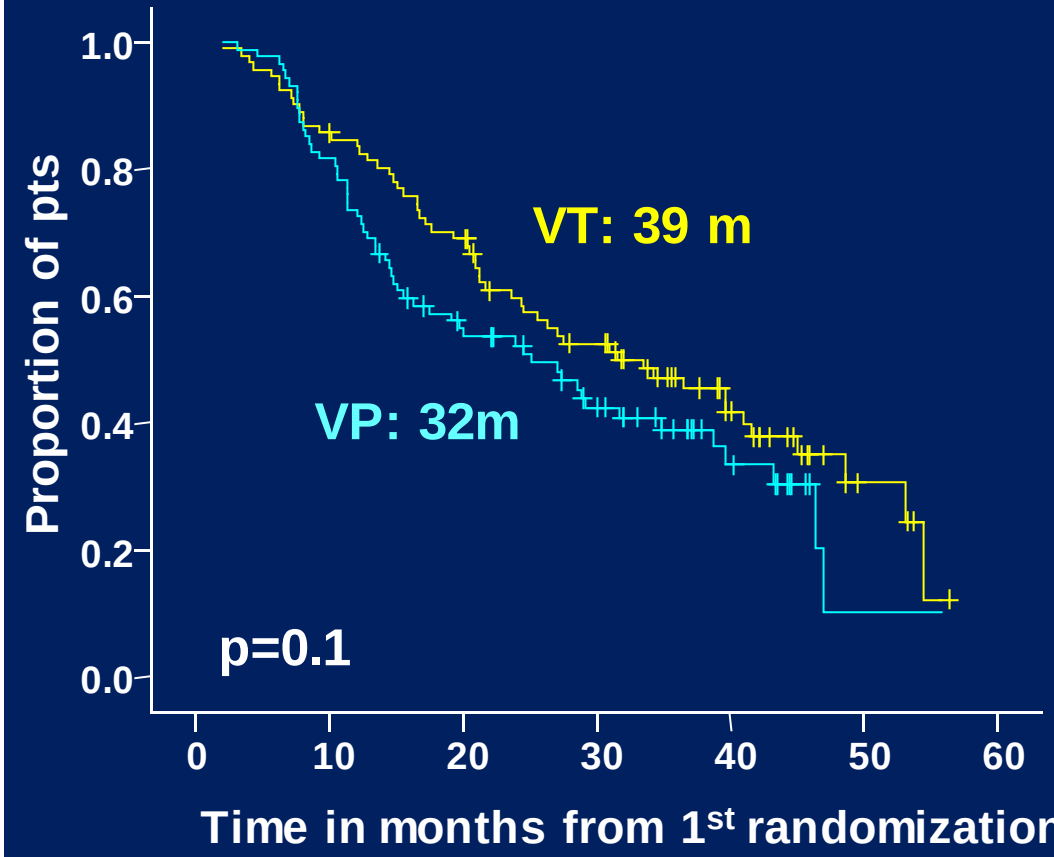
No significant differences between VT/VP

Mateos et al. ASH 2011 (Abstract 477), oral presentation

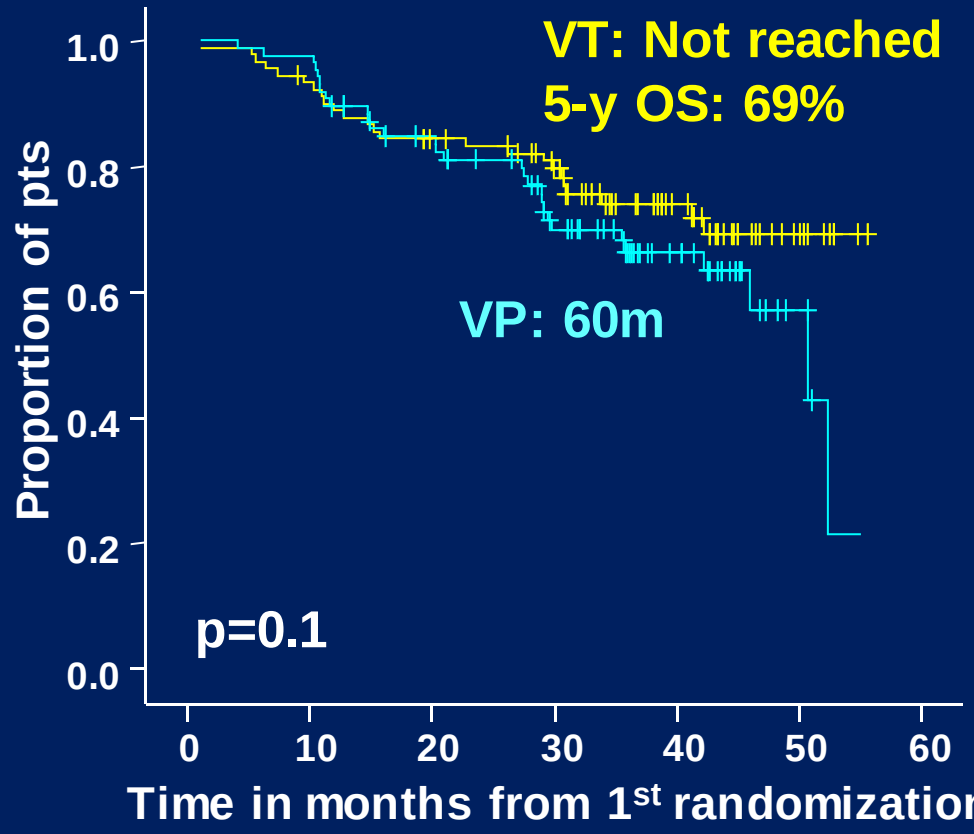
Outcome according to maintenance arm

Median follow-up: 46 m (17-67)

PFS

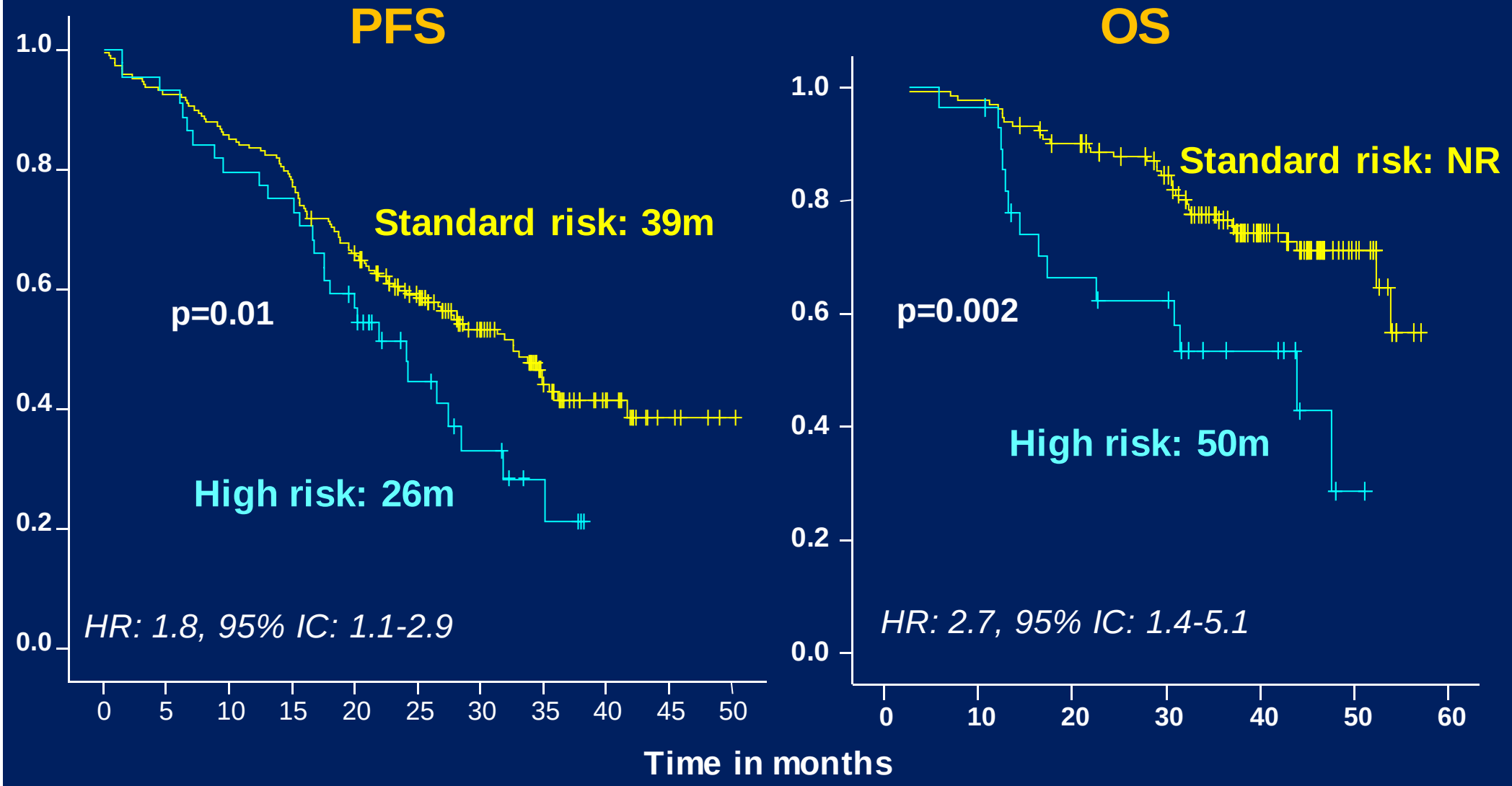


OS



Mateos et al. ASH 2011 (Abstract 477), oral presentation

Outcome according to cytogenetic abnormalities



No significant differences between VT and VP as maintenance regimens

Mateos et al. ASH 2011 (Abstract 477), oral presentation

Toxicity profile

	VT (n=91)	VP (n=87)
Non-Hematologic toxicity, n(%)	Grade 3-4	Grade 3-4
Astenia	2 (2%)	-
Skin Rash	-	-
G-I symptoms	4 (4%)	1 (1%)
Infections	-	-
Thrombotic events	-	-
PN	9 (9%)	3 (3%)
Cardiac events*	2 (2%)	1 (1%)

**Cardiac events: Tacuycardia (1), Hearth atack (2)*

Mateos et al. ASH 2011 (Abstract 477), oral presentation

Toxicity profile

	VT (n=91)	VP (n=87)
Discontinuations, n(%)	**52 (57%)**	**51 (59%)**
Disease Progression	32 (35%)	40(46%)
Toxicity	*12* (13%)*	*8* (9%)*
Others - SMP	6 (7%) 3pts	2 (3%) 1pt
Deaths, n(%)	**24 (26%)**	**30 (35%)**
Disease Progression	19 (20%)	26(30%)
Toxicity	5 (6%)	4 (5%)

Discontinuations due to toxicity: Peripheral neuropathy and cardiac toxicity

Mateos et al. ASH 2011 (Abstract 477), oral presentation

Review of new data in the treatment of patients eligible for transplantation

Phase 3: VTD vs TD (GIMEMA study)
Impact of VTD consolidation

Per-protocol analysis: n=321, received entire treatment program

	VTD	TD	p
CR post-consolidation	61%	47%	0.012
CR/nCR post-consolidation	73%	61%	0.020
Upgrade to CR post-consolidation	30.4%	16.6%	0.030
Landmark analysis from start of consolidation (30 months median follow up)			
3-yr probability of relapse or progression	38%	52%	0.039
3-yr PFS	62%	46%	0.025

- Superior PFS with VTD vs TD consolidation retained across poor prognosis subgroups:
  - t(4;14) and/or del(17q), del(13q)
  - β_2-M >3.5 mg/L, LDH >190 U/L, ISS stage 2 and 3

Cavo *et al*. ASH 2011 (Abstract 1871), oral presentation

Phase 3: VTD vs TD (GIMEMA study)
Impact of VTD consolidation

- No OS difference between two groups

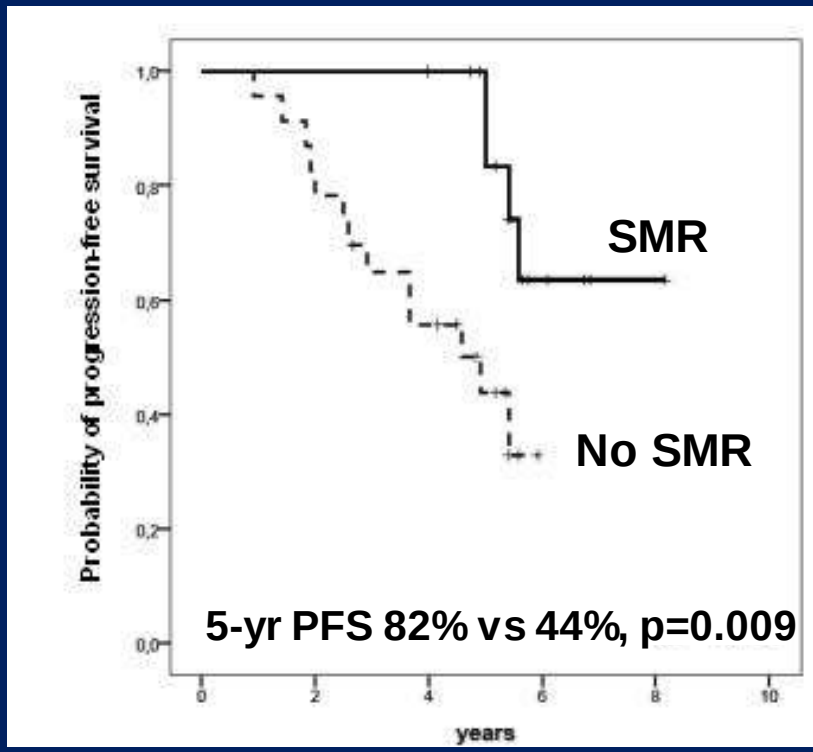
- Both treatments well tolerated
  - Frequency of grade 3/4 AEs comparable in both groups
    - 9.3% VTD, 8.6% TD
  - PN with VTD: 0.6%
  - Skin rash, DVT: 0.6% in each group
  - Patients treated with VTD received 93% of planned doses of bortezomib and thal

Cavo *et al*. ASH 2011 (Abstract 1871), oral presentation

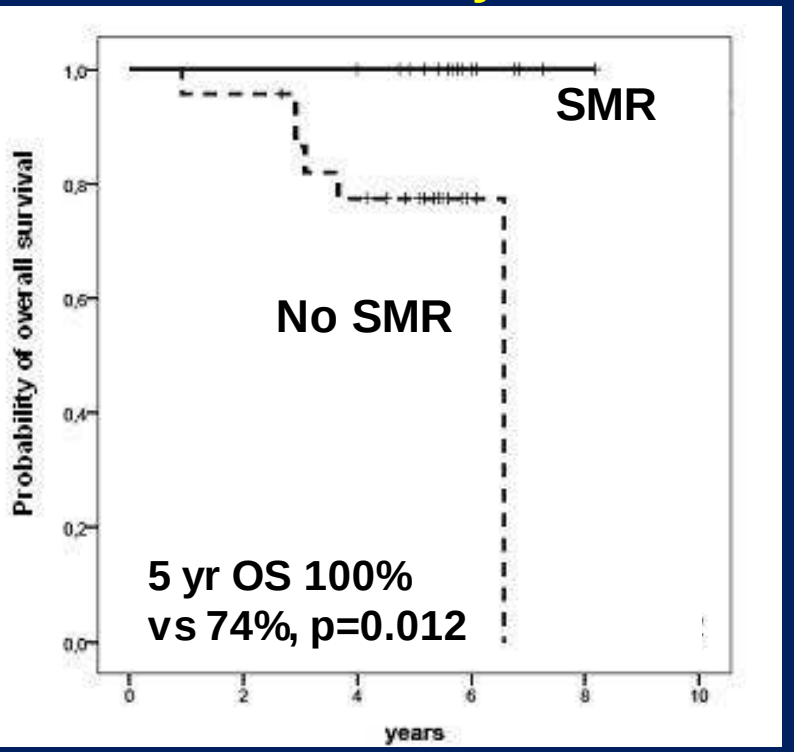
VTD consolidation: long-term follow up

- Impact of MRD detection by RQ-PCR on late recurrences and OS
- Median follow-up: 65 months; n=39

Probability of PFS



Probability of OS



SMR: Standard molecular remission (MRD negativity on two consecutive samples by RQ-PCR)

- No patient with full molecular remission or SMR has died
- Dynamic increase in molecular tumor burden predicts late disease relapses before clinical recurrence

Ladetto et al. ASH 2011 (Abstract 827), oral presentation

Phase 2: VRD induction, ASCT, VRD consolidation, lenalidomide maintenance (IFM 2008)

- Patients (n=31)

%	After VRD induction (3 cycles)	After ASCT	After VRD consolidation (2 cycles)	After Len maintenance (12 months)
sCR	17	36	39	38
CR	6	6	9	10
VGPR	39	26	36	28

- Improvement in responses
  - Consolidation: upgraded response in 26%
  - Len maintenance: no improvement in response rate

Roussel et al. ASH 2011 (Abstract 1872), poster presentation

Phase 3 PETHEMA/GEM trial: Maintenance VT vs Thal vs Interferon alfa-2b

Median follow-up 24 months

	VT	Thal	Interferon-α2b	p
PFS @ 2 years	78%	63%	49%	0.01
Grade 3/4 hematological toxicity	22.2%	16%	21.8%	
PN (grades 1-3)	12.2%	10.1%	0	
Dose reductions	33.3%	33.7	19.5%	
Discontinuation due to toxicity	15.6%	30.3%	18.3%	

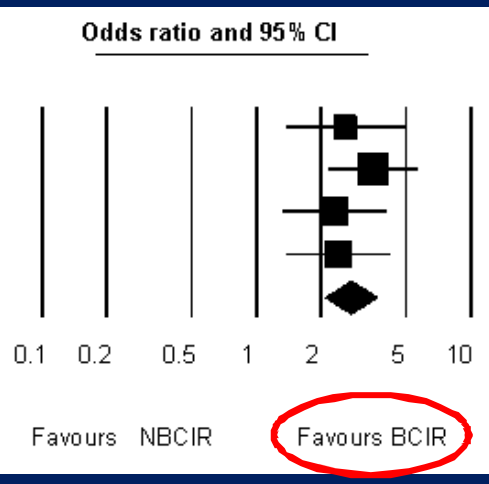
Rosinol et al. ASH 2011 (Abstract 3962), poster presentation

Meta-Analysis: Phase 3 trials of bortezomib containing induction regimens

Impact of bortezomib induction on CR post induction

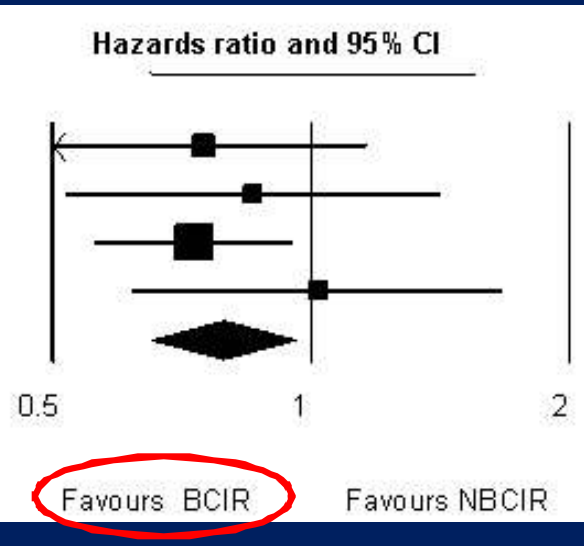
n=2086

Study name	Odds ratio	Lower limit	Upper limit	Relative weight	p-Value
Harousseau, JL	2.596	1.352	4.987	18.30	0.004
Cavo, M	3.500	2.152	5.693	32.95	0.000
Sonneveld, P	2.315	1.317	4.070	24.49	0.004
Rosinol, L	2.422	1.374	4.270	24.27	0.002
Pooled OR	2.739	2.072	3.621		0.000



Impact of bortezomib induction on overall survival

Study name	Hazards ratio	Lower limit	Upper limit	Relative weight	p-Value
Harousseau, JL	0.749	0.483	1.162	19.26	0.197
Cavo, M	0.856	0.516	1.419	14.56	0.545
Sonneveld, P	0.730	0.558	0.956	51.24	0.022
Rosinol, L	1.018	0.618	1.676	14.94	0.945
Pooled HR	0.789	0.651	0.957		0.016

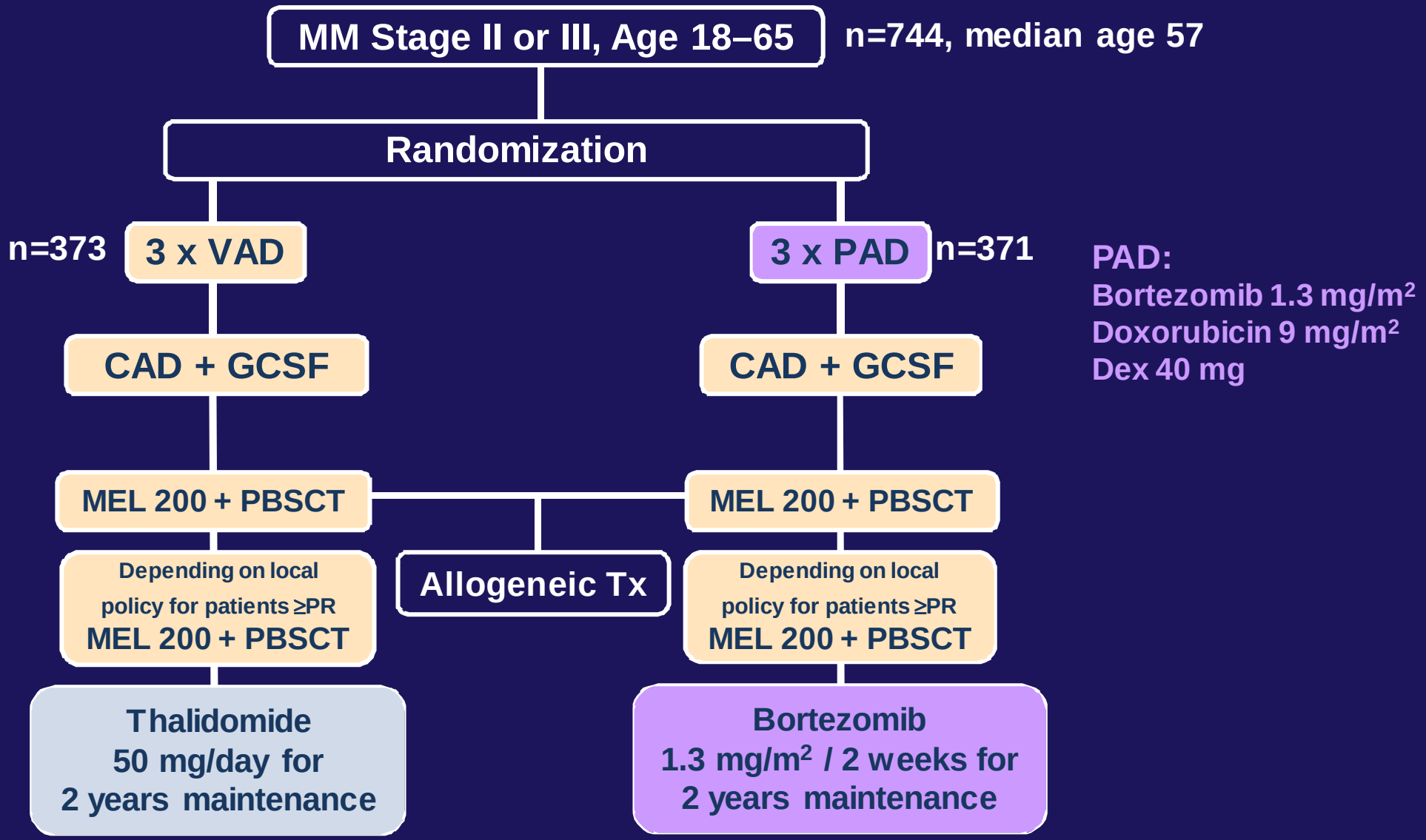


BCIR: bortezomib-containing regimens

Nooka et al. ASH 2011 (Abstract 3994), poster presentation

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

HOVON 65 MM / GMMG-HD4 study



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

HOVON 65 MM / GMMG-HD4 study: Bortezomib Induction and Maintenance Therapy

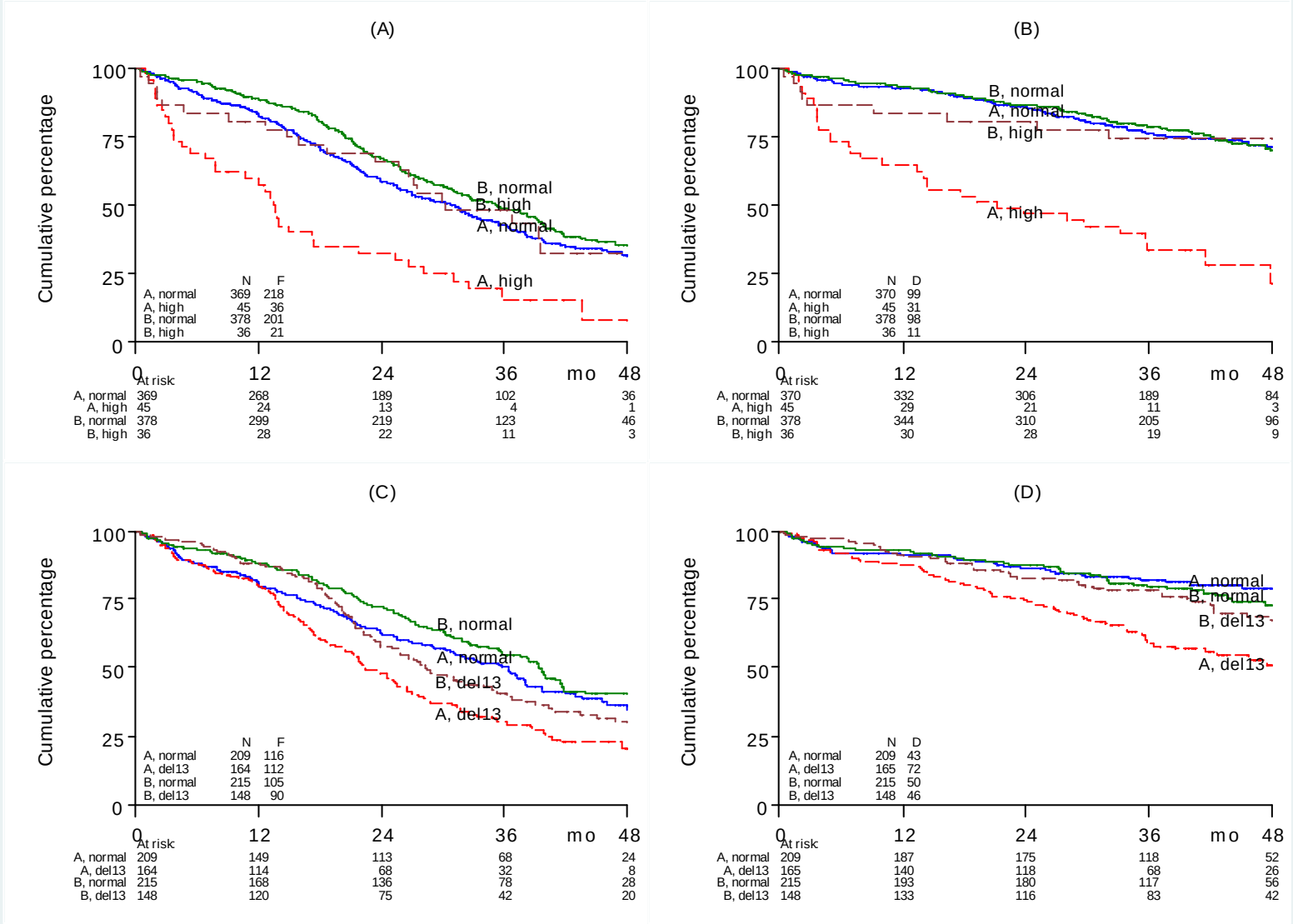
n=744, median age 57

Study details	Median follow up	n	Results			
			≥nCR	≥VGPR	PFS	OS
PAD/HDM/ Bortezomib		205	49%*	76%*	36 m*	Median not reached
vs	39 m					HR=0.73 (0.56-0.96)
VAD/HDM/ Thalidomide		239	34%	55%	27m	p=0.02

*significant difference between arms

Sonneveld et al. ASH 2010 (Abstract 40), oral presentation

HOVON/GMMG study: High-risk groups in both study arms
Renal failure and del 13



Prognostic Impact of Chromosomal Abnormalities on Outcome

	Median PFS (months)			OS at 36 months (%)		
	present	absent	p-value	present	absent	p-value
del(8p21)	27	35	0.096	70	80	0.40
del(13q14)	27	39	0.0023	70	85	0.0001
del(13q14)*	31	40	0.13	85	87	0.055
del(17p13)	18	36	<0.0001	36	83	<0.0001
+1q21	27	39	0.0002	70	82	0.0052
+11q23	36	31	0.45	79	77	0.47
+19q13	36	31	0.19	83	73	0.043
HD*	35	32	0.54	81	75	0.39
t(4;14)	22	36	0.0002	55	82	0.0003
t(11;14)	39	32	0.8	83	77	0.53
t(14;16)	29	35	0.30	83	78	0.11

*del(13q14) without the presence of del(17p13) and t(4;14)

Comparison between both treatment arms

	Median PFS (months)			OS at 36 months (%)		
	Arm B	Arm A	p-value	Arm B	Arm A	p-value
del(8p21)	33	25	0.37	78	65	0.16
del(13q14)	27	25	0.27	81	61	0.072
del(17p13)	26	12	0.024	69	17	0.028
+1q21						10
+11q2						11
+19q1						26
HD*	36	33	0.21	84	78	0.21
t(4;14)	25	22	0.12	66	44	0.37
t(11;14)	40	35	0.33	87	79	0.37

For all analyzed chromosomal aberrations, the median PFS times, as well as the 3-yr OS rates were at least equal or superior in the bortezomib-arm as compared to the standard arm

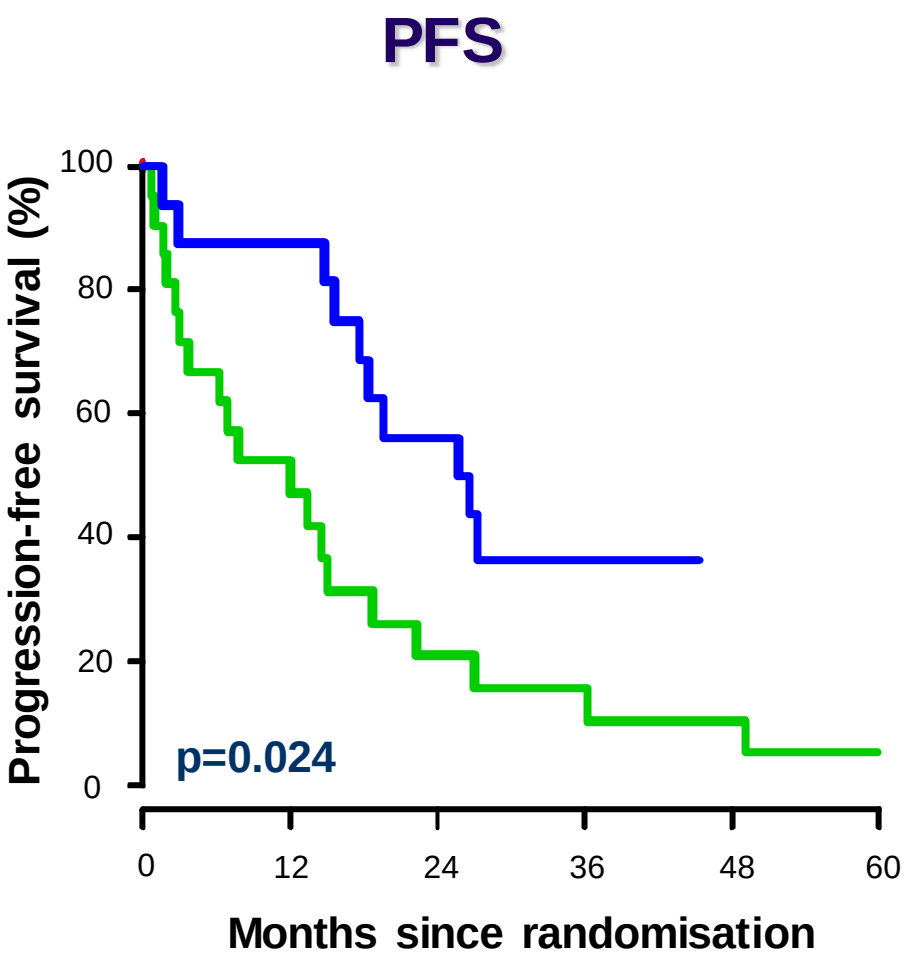
*HD, hyperdiploid

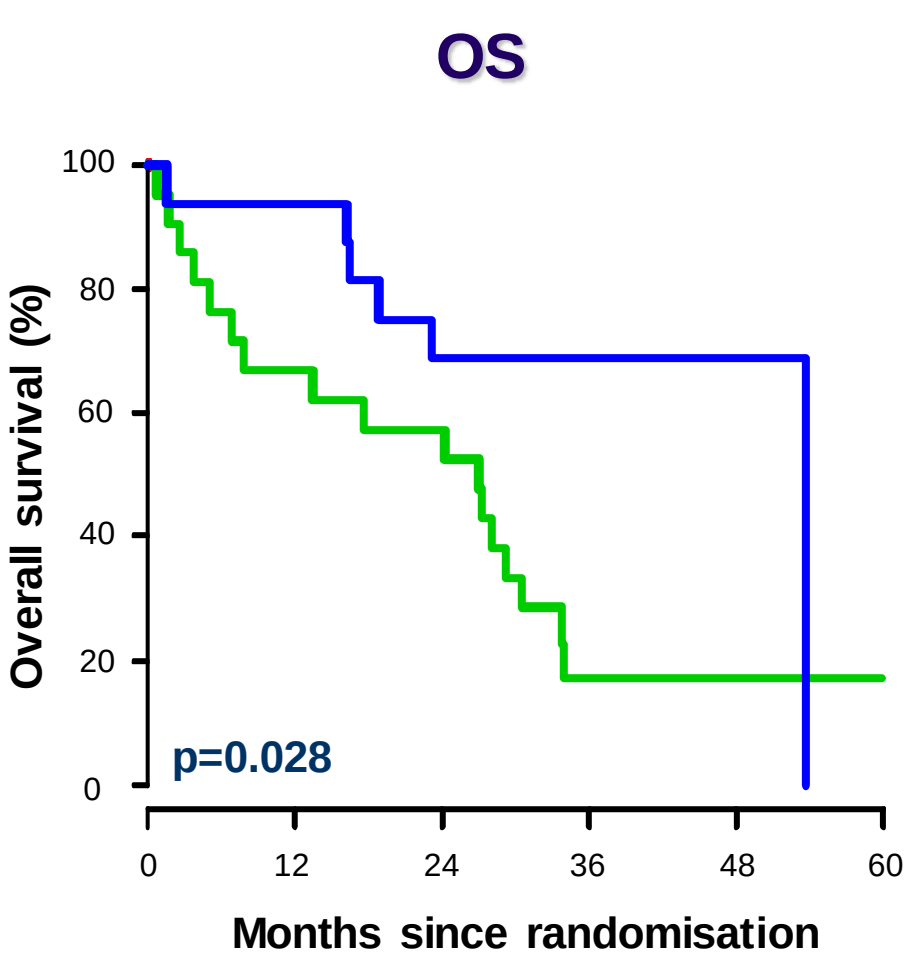
Comparison between both treatment arms

	Median PFS (months)			OS at 36 months (%)		
	Arm B	Arm A	p-value	Arm B	Arm A	p-value
del(8p21)	33	25	0.37	78	65	0.16
del(13q14)	27	25	0.27	81	61	0.072
del(17p13)	26	12	0.024	69	17	0.028
+1q21	28	24	0.22	77	62	0.10
+11q23	39	33	0.27	83	75	0.11
+19q13	38	35	0.41	85	80	0.26
HD*	36	33	0.21	84	78	0.21
t(4;14)	25	22	0.12	66	44	0.37
t(11;14)	40	35	0.33	87	79	0.37

*HD, hyperdiploid

Comparison between both study arms
Deletion 17p13

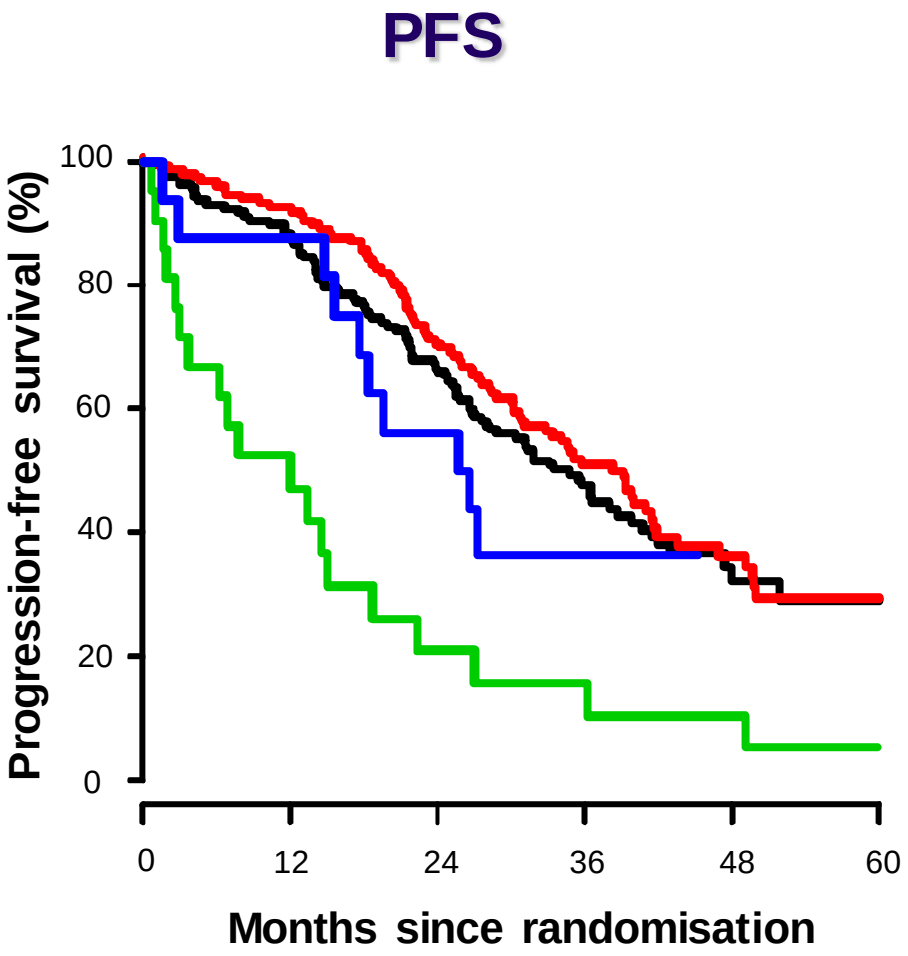


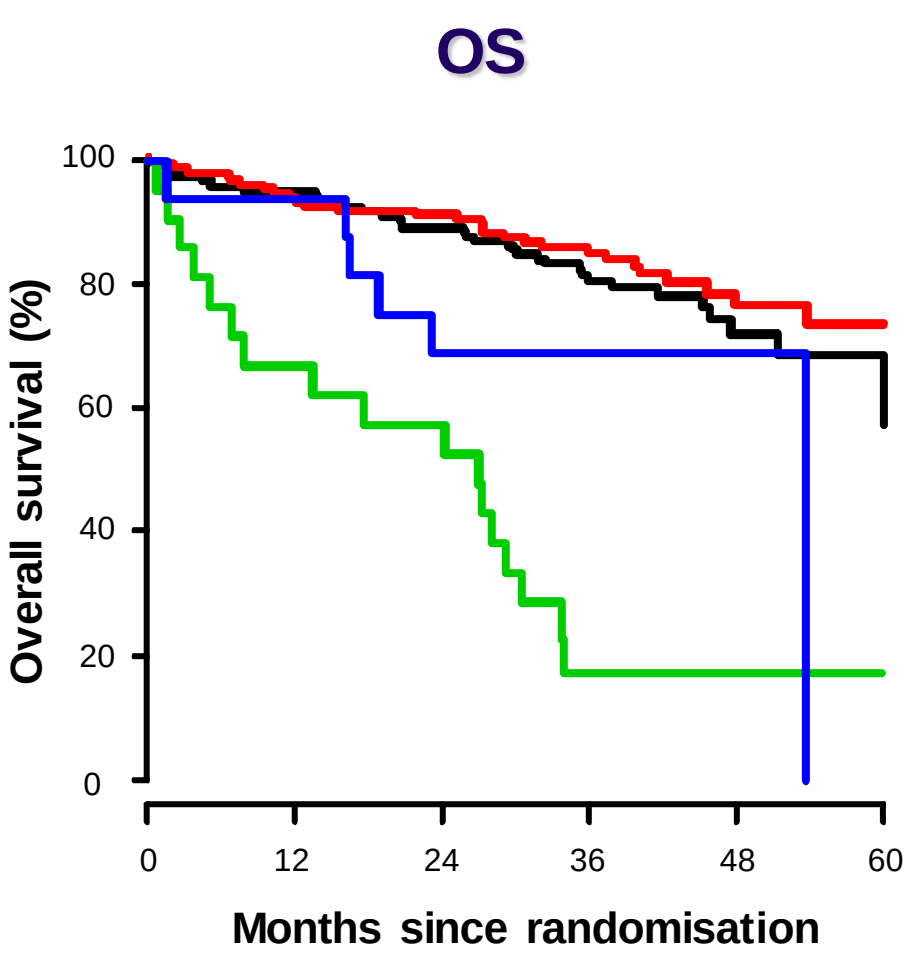


del (17p), arm A (n=21)

del (17p), arm B (n=16)

Comparison between both study arms
Deletion 17p13





del (17p), arm A (without Bortezomib)

del (17p), arm B (with Bortezomib)

no del (17p), arm A (without Bortezomib)

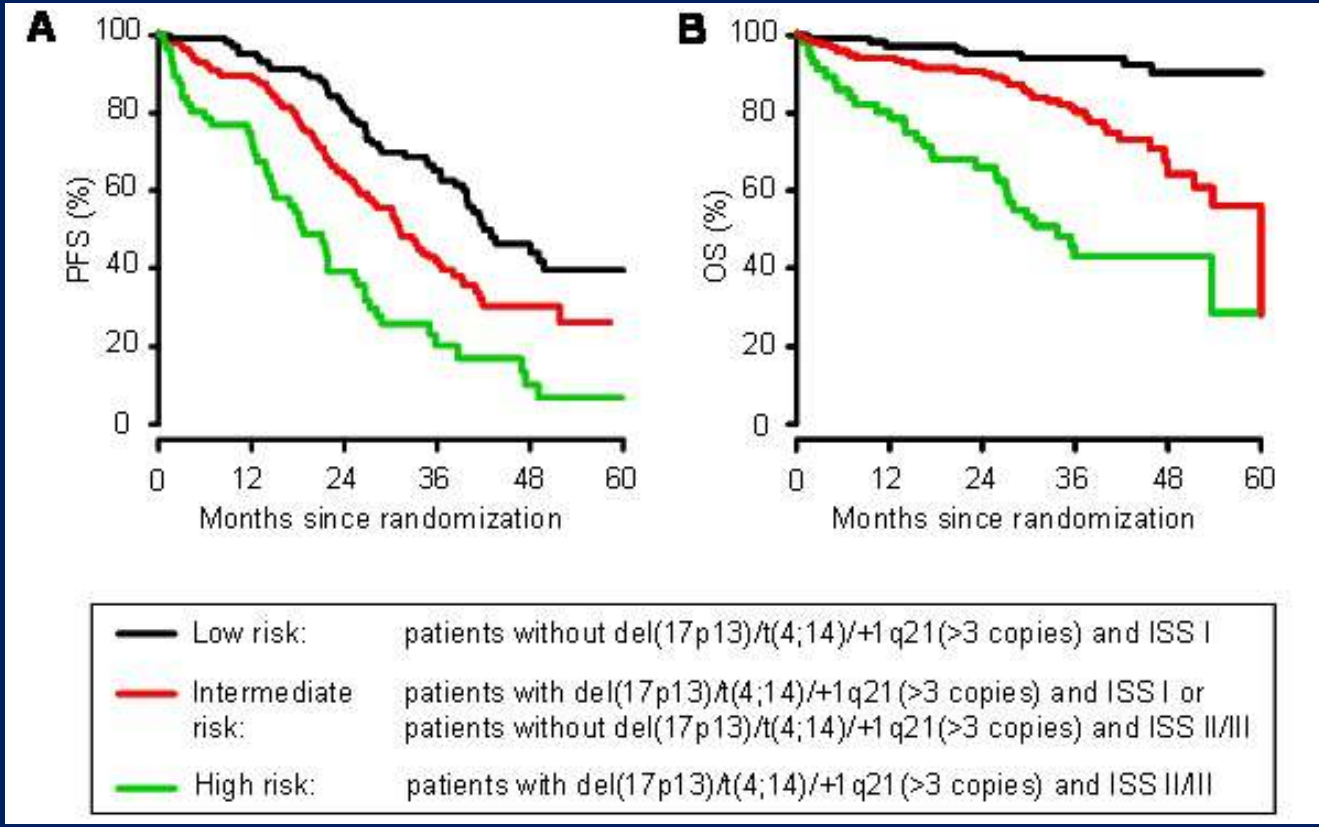
no del (17p), arm B (with Bortezomib)

HOVON-65/GMMG HD4 study: Stratification based on chromosomal aberrations and ISS staging

- **Stratification into 3 groups:**
  - **Low-risk (33%):** absence of del(17p13)/t(4;14)/+1q21 (>3 copies) and ISS I
  - **High-risk (18%):** presence of del(17p13)/t(4;14)/+1q21 (>3 copies) and ISS II/III
  - **Intermediate-risk (49%):** all remaining patients

Neben *et al*. ASH 2011 (Abstract 332), oral presentation

HOVON-65/GMMG-HD4 study: Stratification based on chromosomal aberrations and ISS staging



	Low-risk	Intermediate-risk	High-risk	p
PFS (months)	41.9*	31.1*†	18.7†	*0.0018, †<0.0001
3-year OS	94%*	80%*†	43%†	*0.0001, †<0.0001

Neben *et al*. ASH 2011 (Abstract 332), oral presentation

MRC Myeloma IX long-term follow up

Median follow-up 5.8 years

Non-intensive treatment

	CTDa	MP	p
PFS (months)	13	12	0.003
OS (months)	34	32	0.29

In favorable cytogenetics group, CTDa associated with sign. PFS benefit; no difference in OS

Intensive treatment

	CTD	CVAD	p
PFS (months)	26	24	0.63
OS (months)	72	63	0.19

Morgan et al. ASH 2011 (Abstract 993), oral presentation

MRC Myeloma IX long-term follow up

Median follow-up 5.8 years

	Maintenance		
	Thal	No thal	p
PFS (months)	22	16	< 0.0001
OS (months)	60	60	0.59

- In favorable cytogenetics group: Significant benefit for Thal; no difference in OS
- In unfavorable cytogenetics group: significant negative impact of thal on OS

	Bisphosphonates		
	ZOL	CLO	p
PFS (months)	19	18	0.01
OS (months)	51	46	0.03

Morgan et al. ASH 2011 (Abstract 993), oral presentation

Interaction of response and FISH-based risk stratification to better define clinical outcome

Analysis of CR in context of other prognostic factors in MRC IX (intensive arm)

- Comparable CR rates in pts with and without adverse FISH
- CR associated with improved PFS in pts without adverse FISH and ISS I
- Trend towards improved PFS in pts with adverse FISH and ISS II / III
- Multivariate analysis (pts in CR)
  - Adverse FISH most significant factor for impaired PFS and OS
  - > 1 adverse FISH lesion: especially high risk of progression or death

- **Conclusion**
  - Impaired outcome due to adverse FISH not overcome by achievement of CR with CTD
  - Quick progression following end of therapy → need alternative treatment strategies aimed at maintaining responses

adverse FISH: t(4;14), t(14;16), t(14;20), +1q or 17p-

Boyd et al. ASH 2011 (Abstract 1823), poster presentation

Phase 2: RAD induction + tandem autoSCT / auto + allo SCT (DSMM XII)

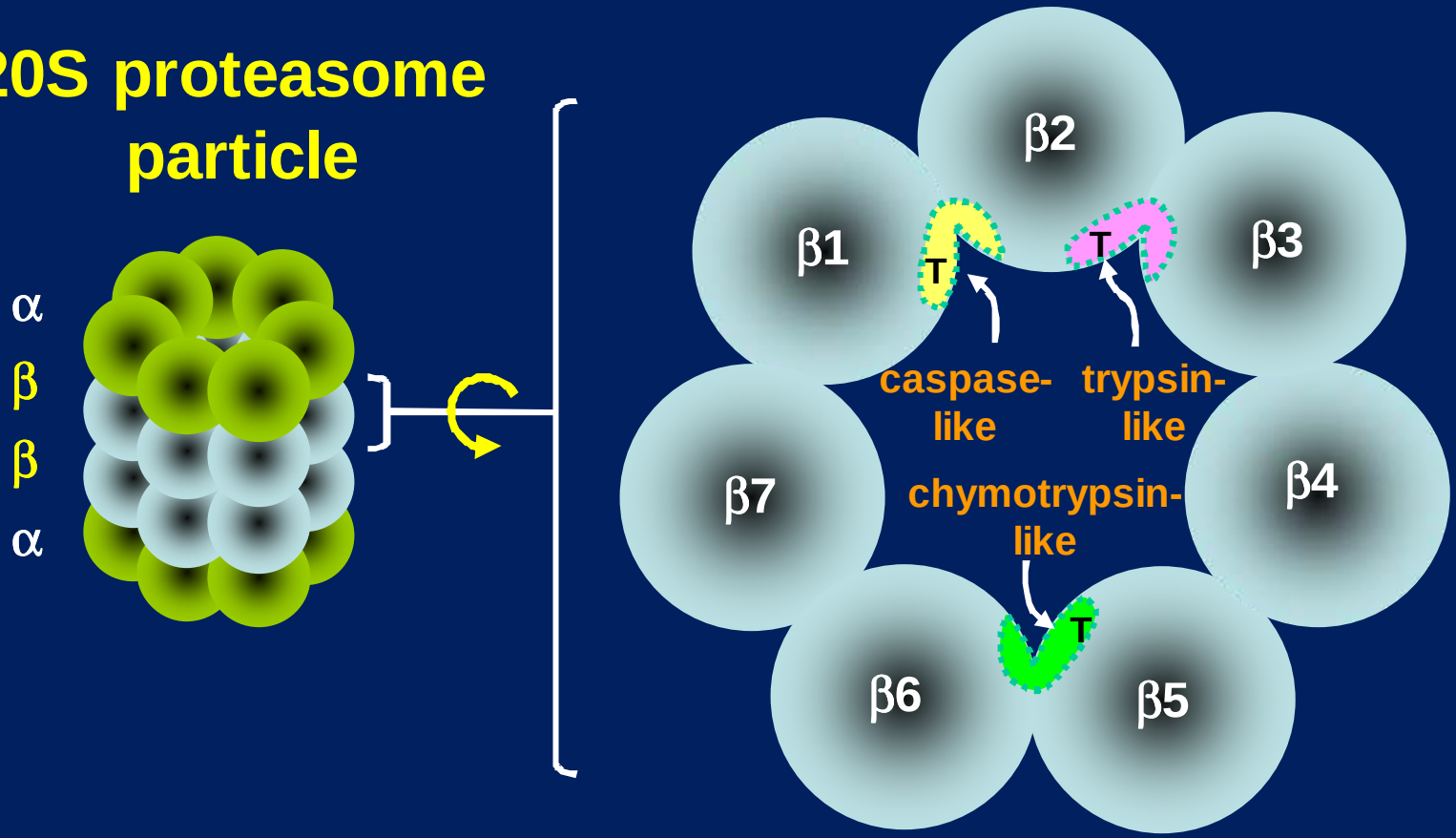
- **Treatment**
  - RAD induction (4 cycles)
  - Two transplants: tandem autoSCT or auto + alloSCT for pts with ≥ 1 cytogenetic or serologic risk factor
  - Lenalidomide maintenance: 12 months

- **Results**
  - n=148 enrolled, n=52 evaluable for post-induction response
  - ORR 79%, ≥ VGPR 52%, CR/sCR 13%
  - Severe treatment-emergent AEs 35%
    - Hematologic events 4%
    - Infections 8%
    - Venous thromboembolism 6%

Knop et al. ASH 2011 (Abstract 3967), poster presentation

Carfilzomib irreversibly inhibits the proteasome

20S proteasome particle



β-subunit ring

Three distinct N-terminal threonine protease active sites

IC_{50}s (nM)	Chymotrypsin-like	Caspase-like	Trypsin-like
Carlfizomib	6	2400	3600
Bortezomib	7	74	4200

Phase 2: Carfilzomib + Thal + Dex
(CARTHADEX) EMN trial

- Aim: evaluate carfilzomib + thal + Dex during induction and consolidation in newly diagnosed MM
- Patients (n=45), median age 57 years
- Responses after induction
  - RR 84%, CR/sCR 16%, VGPR 29%, PR 38%

	Grade 1/2	Grade 3
PN	24%	0
Tumor lysis syndrome	0	4%
GI	4%	4%
Skin	2%	2%
Infection	4%	4%

- Conclusion: Carfilzomib + thal + dex during induction and consolidation is feasible and effective

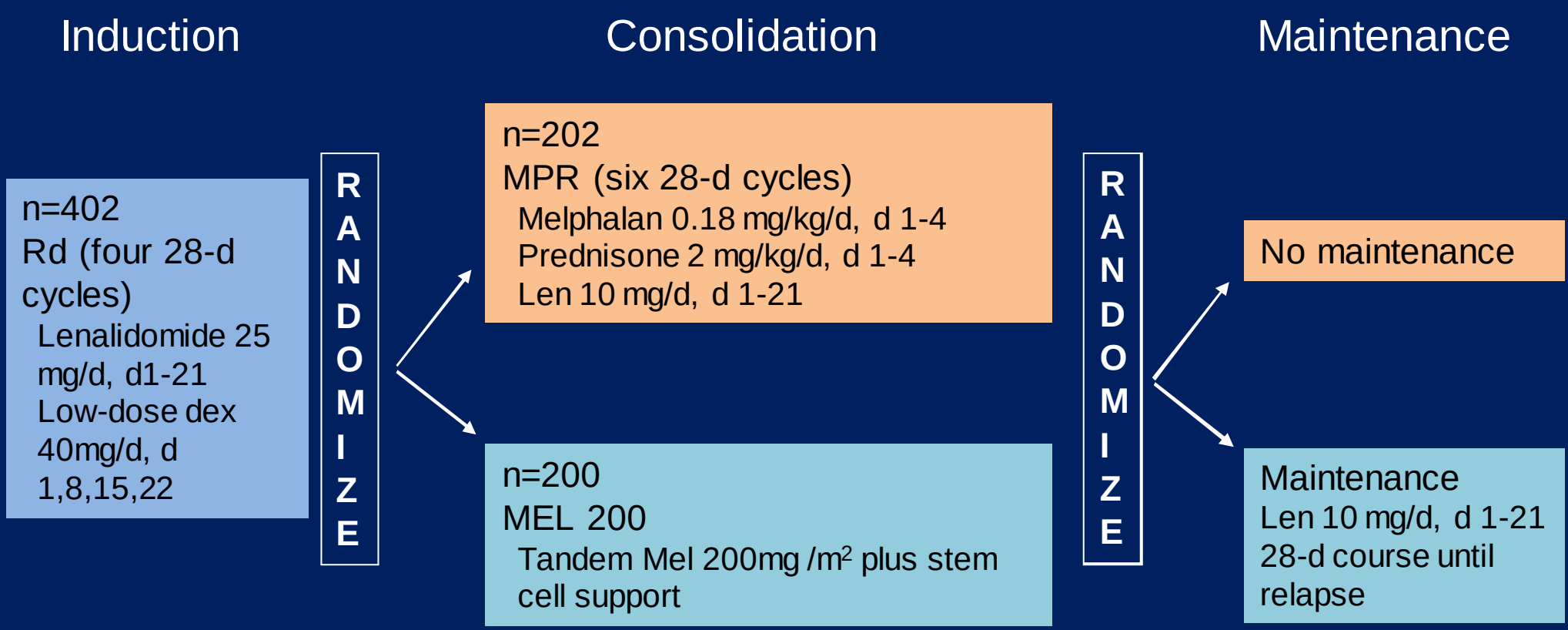
Sonneveld et al. ASH 2011 (Abstract 633), oral presentation

What are the conclusions?

- Bortezomib based induction treatment is the standard of care in many countries in Europe
- Long term Bortezomib treatment improves the prognosis of bad FISH-cytogenetic features
- Thalidomide maintenance improves PFS in the MRC-trial, no impact on OS
- Zoledronacid is superior to Clodronate in terms of PFS and EFS
- Lenalidomide based induction is effective and well tolerated
- Carfilzomib based induction and consolidation is effective and has low PNP

What is the role of ASCT?

Phase 3: MPR versus tandem ASCT



Primary end point: PFS

Palumbo et al. ASH 2011 (Abstract 3069), poster presentation

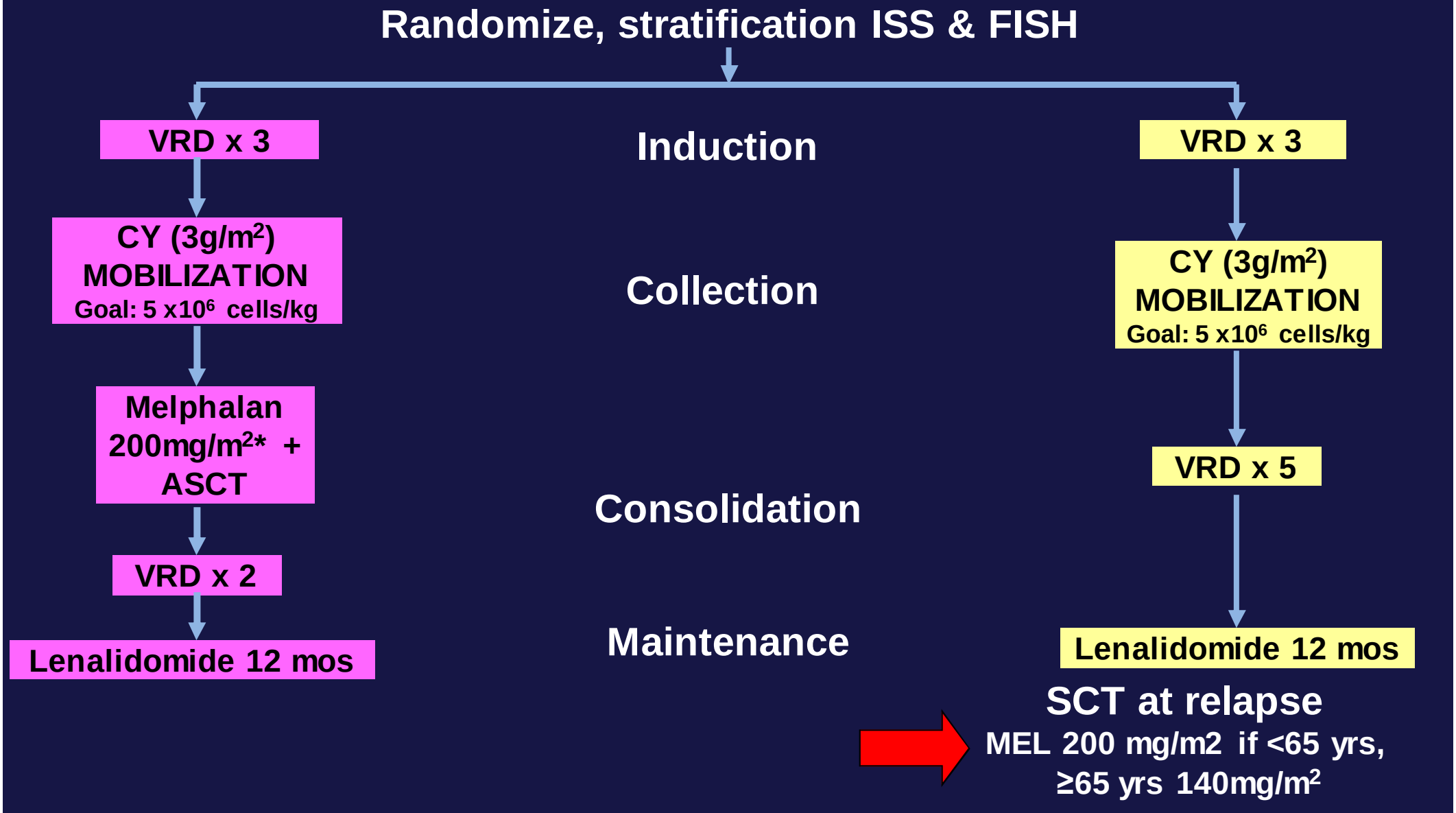
Phase 3 study: MPR versus tandem ASCT

Median follow up 26 months

	MPR (n=202)	MEL 200 (n=200)	p
CR	20%	25%	0.49
≥VGPR	60%	58%	0.24
2-year PFS	54%	73%	<0.001
2-year OS	87%	90%	0.19
Standard-risk patients 2-year PFS	46%	78%	0.007
High-risk patients 2-year PFS	27%	71%	0.004
Patients who achieved CR 2-year PFS	66%	87%	<0.001
Patients who achieved PR 2-year PFS	56%	77%	<0.001
Gr 3/4 neutropenia	55%	89%	<0.001
Gr 3/4 infections	0%	17%	<0.001
Gr 3/4 gastrointestinal toxicity	0%	21%	<0.001
DVT	2.44%	1.13%	0.43
Second tumors	0.5%	1.5%	0.12

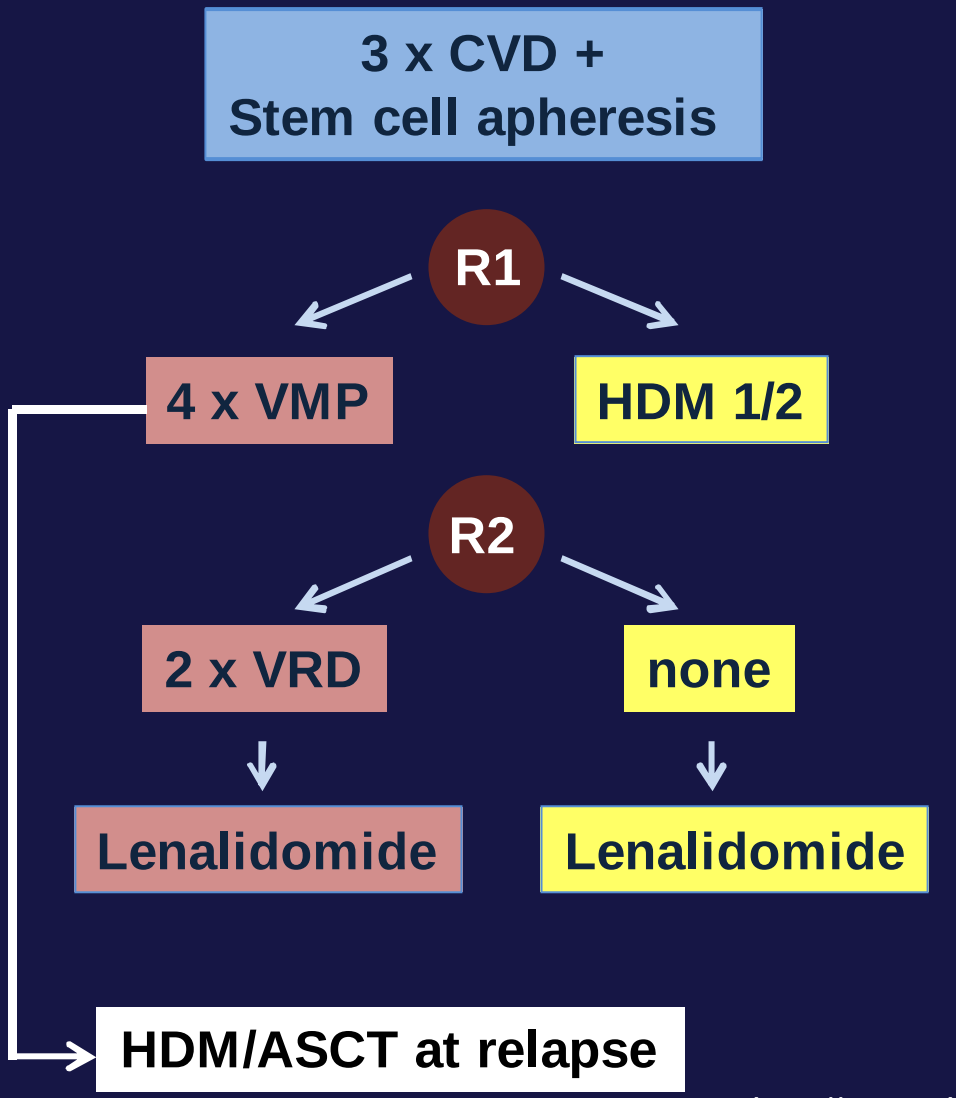
Palumbo et al. ASH 2011 (Abstract 3069), poster presentation

IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)



http://www.clinicaltrials.gov/ct2/show/NCT01208662?term=nct01208662&rank=1

Novel agents alone versus intensive therapy + novel agents: European Intergroup trial



Registration
Induction

Stem cell mobilization in all pts

Consolidation

Maintenance
until relapse

http://www.clinicaltrials.gov/ct2/show/NCT01208766?term=Sonneveld&rank=2

Strategies to improve the tolerability of treatment

Strategies to improve the tolerability of treatment

- Changing the route of administration
- Changing treatment schedules
  - Reduction in frequency of dosing
  - Reduction in drug dosage

Pharmacokinetics (PK) and pharmacodynamics (PD) of subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: effects of subcutaneous injection site and concentration, and patient characteristics

Moreau et al. ASH 2011 (Abstract 1863), poster presentation

Phase 3 trial: SC versus IV bortezomib

- **Efficacy**
  - Comparable efficacy for SC and IV administration
  - Improved safety profile with SC administration
- **Pharmacokinetics / Pharmacodynamics**
  - Systemic exposure equivalent with SC and IV administration
  - Lower C_{max} and longer T_{max} with SC versus IV bortezomib
  - No effect of SC injection concentration on PK or PD parameters
  - PD parameters of proteasome inhibition similar for SC and IV bortezomib

Moreau et al. Lancet Oncol 2011;12(5):431-40

Moreau et al. ASH 2011 (Abstract 1863), poster presentation

Phase 3 trial: SC versus IV bortezomib

- **PK/PD parameters by injection site**
  - **No difference between administration in thigh or abdomen regarding PK/PD parameters**

- **Effect of demographic covariates on bortezomib exposure**
  - **No differences in bortezomib exposure related to**
    - **Body mass index (BMI)**
    - **Body surface area (BSA)**
    - **Age**

Moreau et al. ASH 2011 (Abstract 1863), poster presentation

Once-weekly administration of bortezomib

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-weekly bortezomib administration								
VISTA[1-3,7]	71%	30%	21.7m	68.5%	47%	13%	14%*	34%
VMP with once-weekly bortezomib administration								
GIMEMA[4,5,7]	79%	23%	27m	87%	22%	2%	4%	17%
PETHEMA/GEM[6,7]	80%	20%	34m	74%	n/a	7%	n/a	12%†

*3% discontinued VMP; 11% selectively discontinued bortezomib due to PN

†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
7. Mateos et al. Haematologica 2011; 96 (s1): S81 (Abstract P-175); poster presentation at IMW 2011

Improving tolerability with dose reduction

- **VD versus vtD as induction treatment prior to ASCT[1]**
  - **Significantly reduced incidence of PN with vtD**
    - **Grade ≥ 2 PN: 34% VD arm vs 14% vtD (P=0.001)**
- **Low-dose versus high-dose thalidomide for advanced MM[2]**
  - **100 mg/day better tolerated than 400 mg/day**
    - **Significantly lower rates of high-grade somnolence, constipation, nausea/vomiting and PN**
- **Len 15 mg / Dex 20 for relapsed MM > 75 years of age[3]**
  - **45 patients, ORR : 65%, PFS 14 months**

1. *Moreau et al. Blood 2011;118(22):5752-8*
2. *Yakoub-Agha et al. Eur J Haematol 2011, Oct 25 [Epub]*
3. *Touzeau et al. Leuk Lymphoma 2012, Jan 2 [Epub]*

What are the conclusions?

- New route of administration of Bortezomib available in 2012

- Once-a-week infusion : improvement of tolerability, maintenance

- Role of maintenance ?

- Dose reduction useful in combinations

New developments in high-risk MM

A high-risk survival classifier for MM

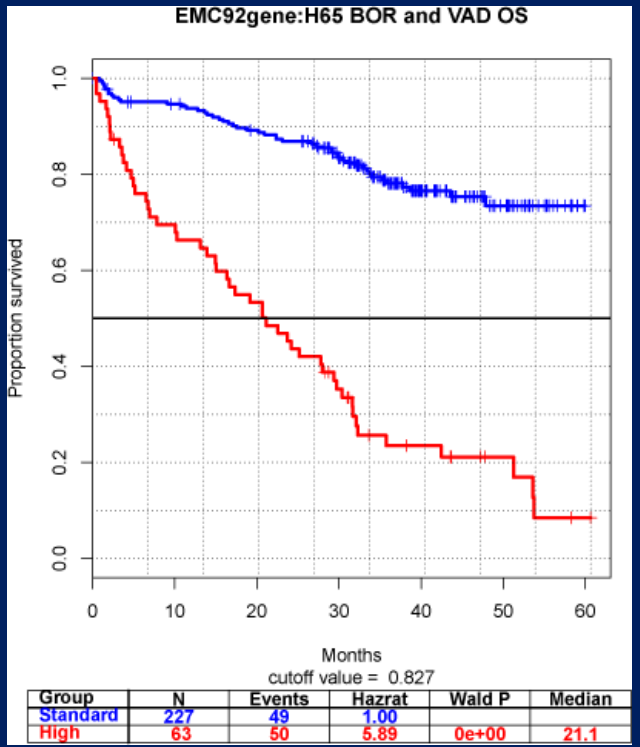
- **Generation of a high-risk gene signature (EMC-92-gene signature) using HOVON65/GMMG-HD4 data**

- **EMC-92-gene signature could identify significantly shorter survival in**
  - **patients with newly diagnosed MM (transplant-eligible and non-transplant-eligible)**
  - **patients with relapsed disease**

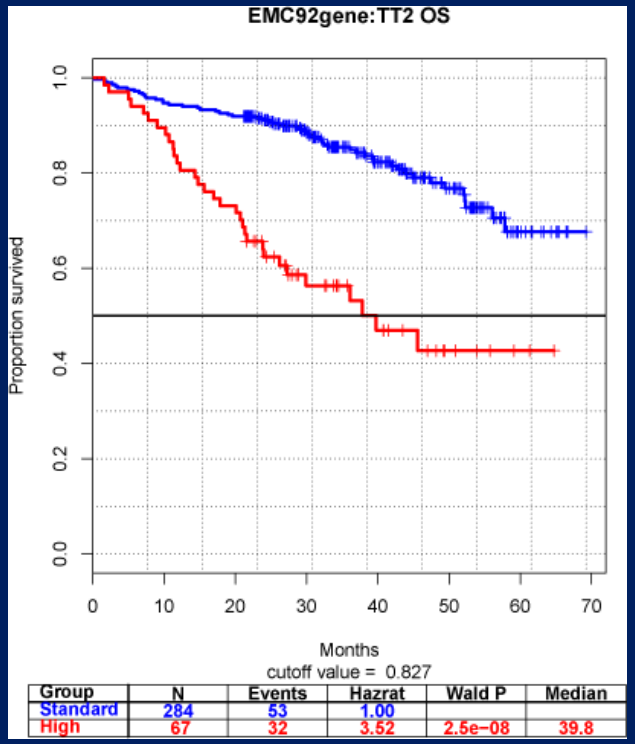
- **Good performance in comparison to other published high-risk gene signatures**

Kuiper *et al*. ASH 2011 (Abstract 1800), poster presentation

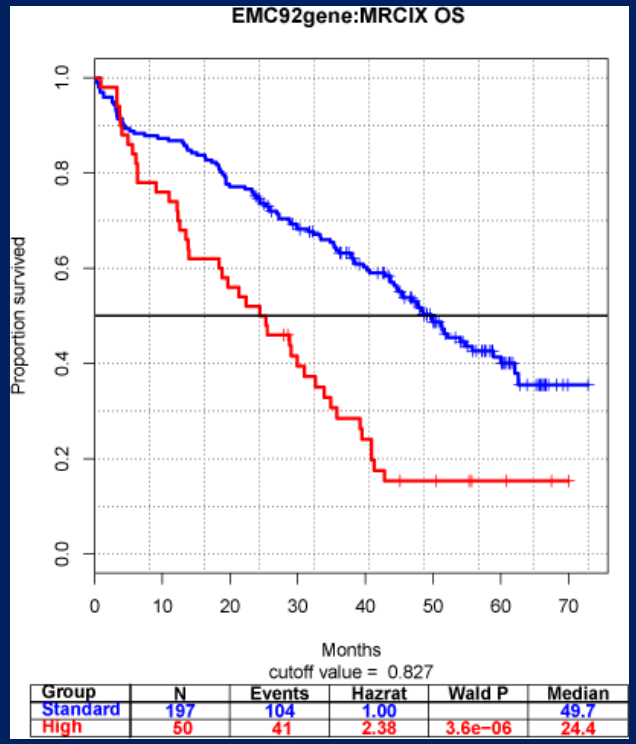
Efforts to improve risk stratification using GEP profiling



Group	N	Events	Hazrat	Wald P	Median
Standard	227	49	1.00		
High	63	50	5.89	0e+00	21.1



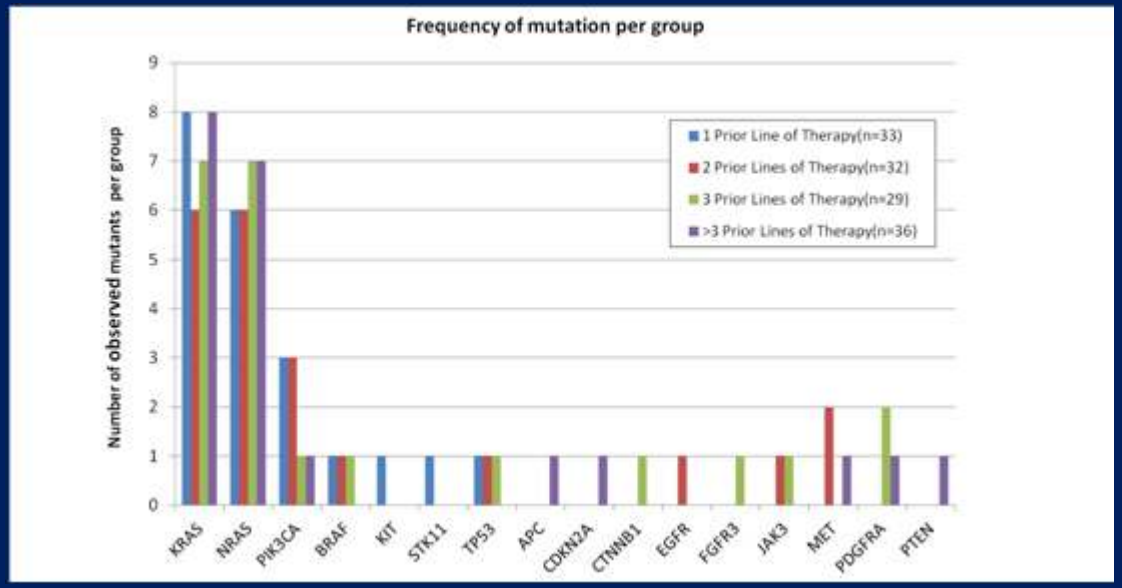
Group	N	Events	Hazrat	Wald P	Median
Standard	284	53	1.00		
High	67	32	3.52	2.5e−08	39.8

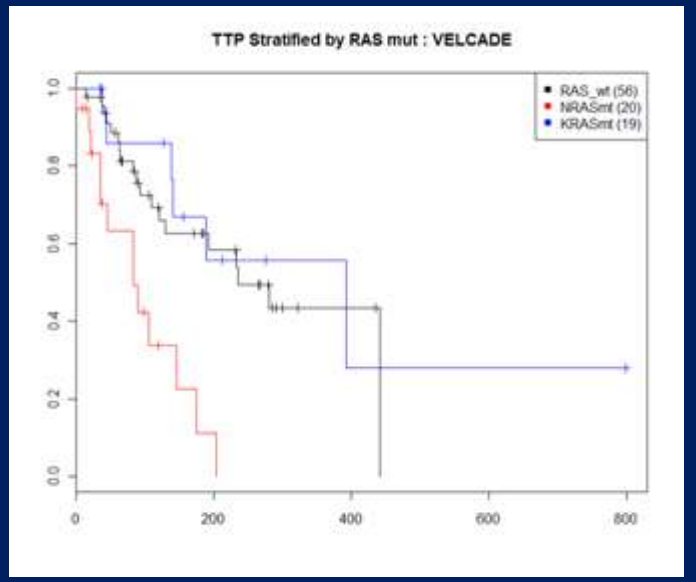


Group	N	Events	Hazrat	Wald P	Median
Standard	197	104	1.00		49.7
High	50	41	2.38	3.6e−06	24.4

Kuiper *et al*. ASH 2011 (Abstract 1800), poster presentation

Frequency of mutations detected by prior line of therapy in 133 MM samples in APEX/SUMMITT





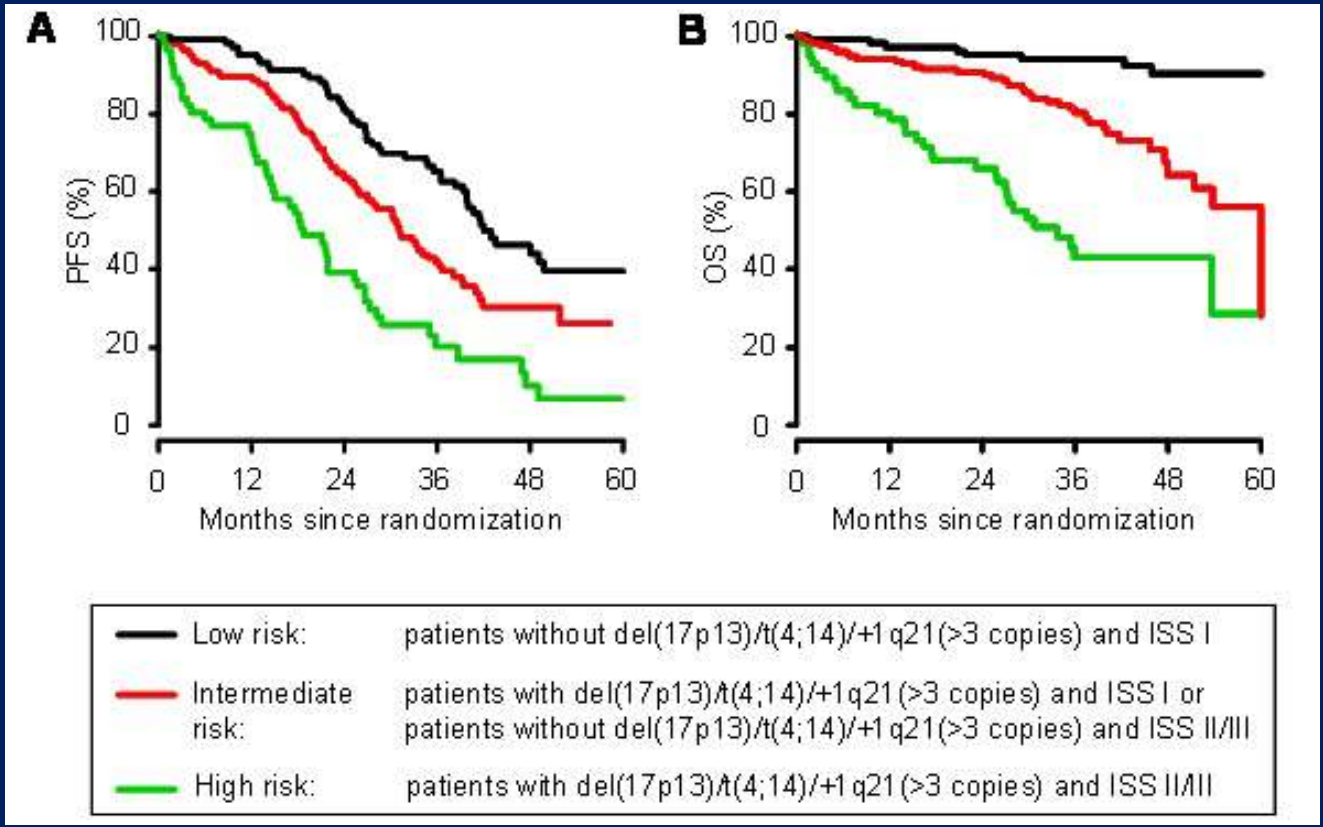
- **Screening of pre-treatment tumor samples from 133 MM patients revealed mutations in 16 different genes**
- **Genes of the RAS/RAF pathway were mutated in 45.9% of cases.**
- **Of these, the most common mutations were detected in KRAS (24.1%) and NRAS (19.5%).**

Cox Proportional-Hazards :

Variable	exp(coef)	p-value
KRAS	**0.828**	**0.69**
NRAS	**3.9**	**3.5×10^{-4}**

Mulligan *et al*. ASH 2011, poster presentation

HOVON-65/GMMG HD4 trial: Stratification of myeloma patients based on chromosomal aberrations and ISS staging



	Low risk (33%)	Intermediate risk (49%)	High risk (18%)	p
PFS (months)	41.9*	31.1*†	18.7†	*0.0018, †<0.0001
3-year OS	94%*	80%*†	43%†	*0.0001, †<0.0001

Neben *et al*. ASH 2011 (Abstract 332), oral presentation

Diffuse pattern of bone marrow involvement in MRI associated with high risk cytogenetics and poor outcome

- Analysis of pattern of marrow involvement with MRI (n=203, newly-diagnosed)
  - Normal (14%): no evidence of abnormal signal
  - Focal (42%): localized areas of abnormal marrow
  - Diffuse (39%): normal bone marrow completely replaced

	Diffuse	Focal	Normal	p
del17p	22%	10%	0	0.04
add1q21	37%	13%	15%	0.038
del13q	48%	28%	24%	0.056
high risk cytogenetics [any of del17p, add1q21, t(4;14) or t(14;16)]	56%	31%	22%	0.012
Median OS (months)	37	57	102	<0.001

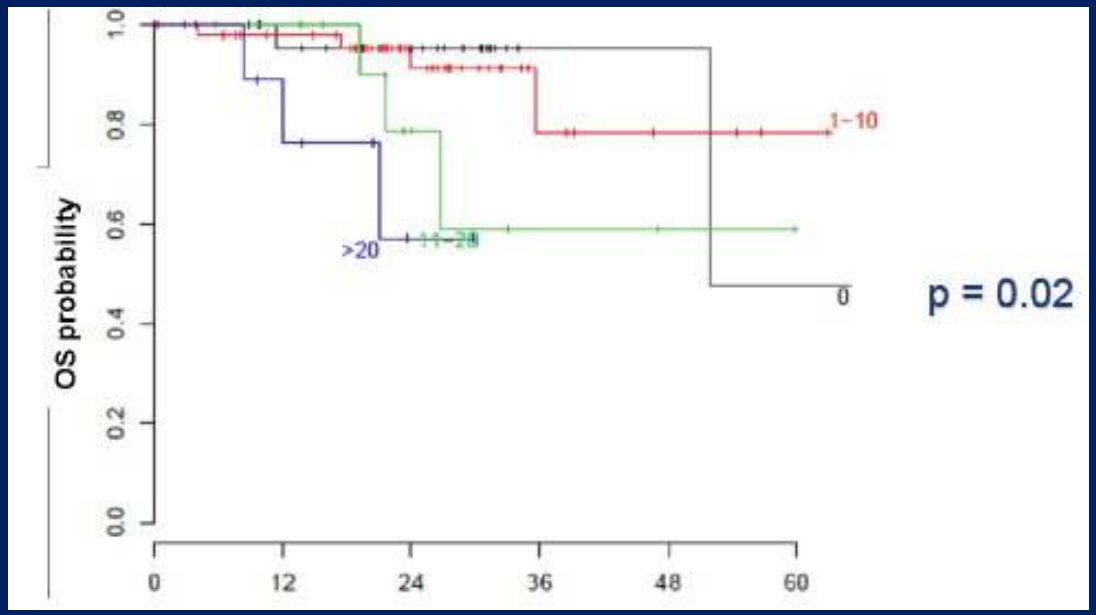
- Conclusions
  - Strong correlation of diffuse pattern with poor OS, even with novel agents
  - Importance baseline MRI in all patients with symptomatic disease

Moulopoulos et al. ASH 2011 (Abstract 3920), poster presentation

Prognostic significance of persisting focal lesions after ASCT

- **Study details: whole body MRI conducted before systemic treatment and post-ASCT**

OS probability for patient groups according to number of focal lesions at second MRI (post-ASCT)



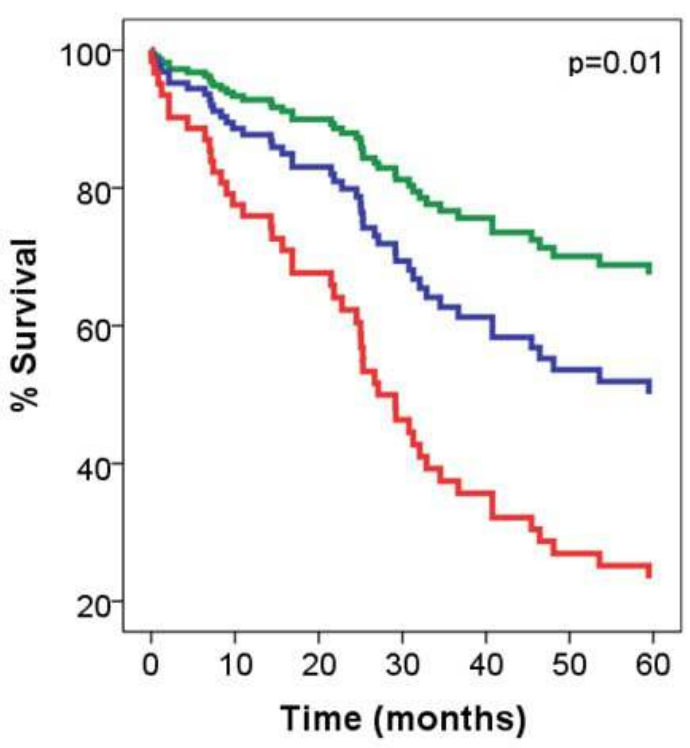
- **Number of focal lesions after ASCT had significant impact on OS**
- **Importance of measuring residual disease after systemic treatment**

Hillengass *et al*. ASH 2011 (Abstract 1812), poster presentation

Prognostic information derived from serum heavy/light chain and free light chain measurements

- Highly abnormal HLC ratio associated with significantly reduced OS
- Monitoring pts with FLC and HLC assays showed significant changes in clonal protein production

- Risk stratification model using highly abnormal HLC and FLC ratios:



0 risk factors (FLC ratio>0.1 or <30 and HLC ratio>0.022 or <45)

1 risk factor (FLC ratio<0.1 or >30 or HLC ratio<0.022 or >45)

2 risk factors (FLC ratio<0.1 or >30 and HLC ratio<0.022 or >45)

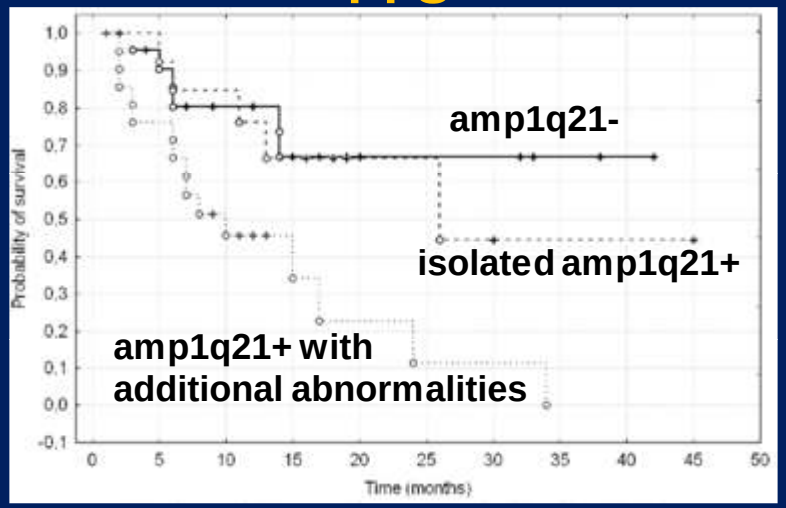
Ludwig *et al*. ASH 2011 (Abstract 2883), poster presentation

Novel agents and cytogenetic abnormalities

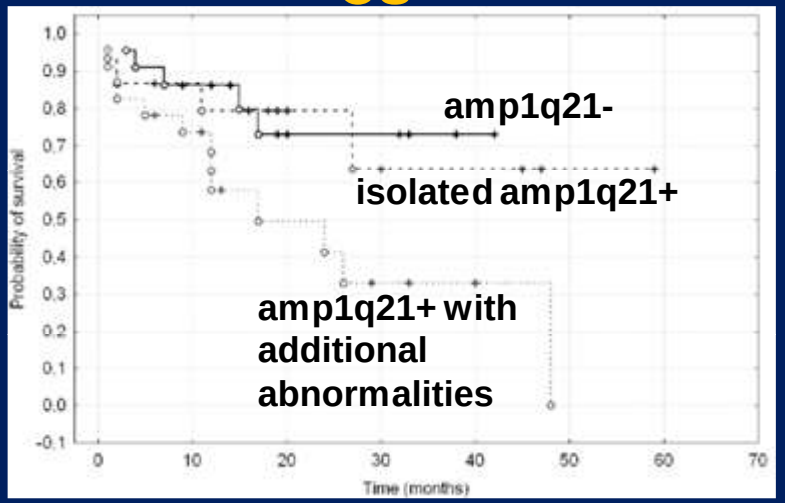
Novel agents and cytogenetic abnormalities: thalidomide

- n=79, newly diagnosed, treated with CTD (n=59) +/- ASCT, MPT (n=20)
- Cytogenetic abnormalities:
  - amp1q21 (49%), del13q14 (48%), t(4;14) (20%), del17p13 (16%)
  - amp1q21 + del13q14 (30%)
  - amp1q21 + t(4;14) (15%)
  - amp1q21 + del17p13 (6%)

PFS



OS



- amp1q21 + other abnormalities associated with shortened PFS and OS
- Thal-based regimens should not be recommended in these patients

Grzasko et al. ASH 2011 (Abstract 2874), poster presentation

Novel agents and cytogenetic abnormalities: bortezomib

- **t(4;14):**
  - **Bortezomib improves outcomes compared to conventional treatments[1]**

- **del17p:**
  - **Remains challenging, but**

    Analysis of HOVON/GMMG trial[2]

    - **Adverse impact of del(17p13) on PFS and OS could be significantly reduced by bortezomib-based treatment**

	With bortezomib	Without bortezomib	p
Median PFS	26.2 months	12 months	0.024
3-year OS	69%	17%	0.028

[1]Reece DE. ASH 2011 Educational Session; ASH Education Program Book 2011:197-204
[2]Neben et al. Blood 2011; Published online before print December 8, 2011

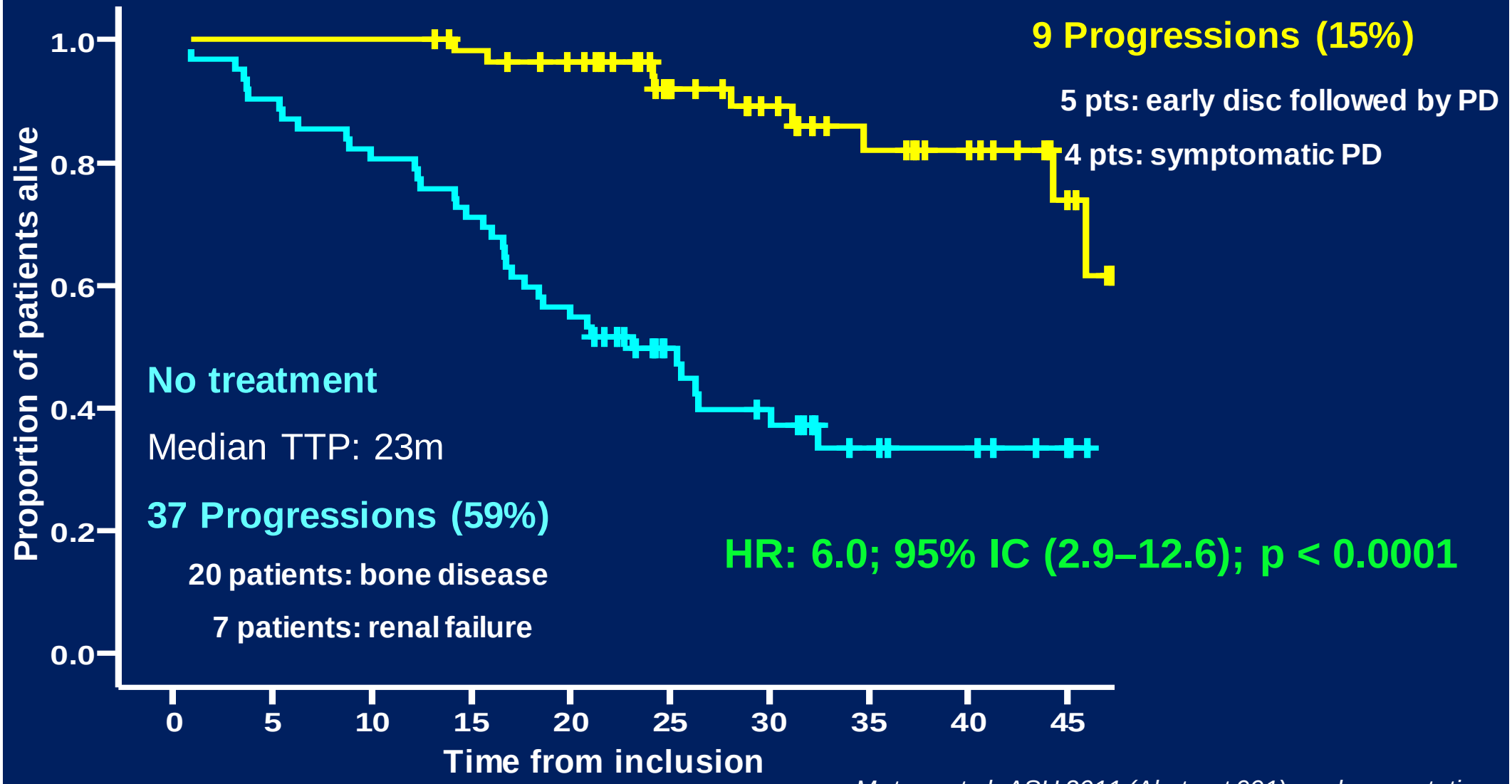
Lenalidomide/dex versus therapeutic abstention in high-risk smoldering MM

Mateos et al. ASH 2011 (Abstract 991), oral presentation

Len-dex vs no treatment: TTP to active disease

(n = 119) ITT analysis

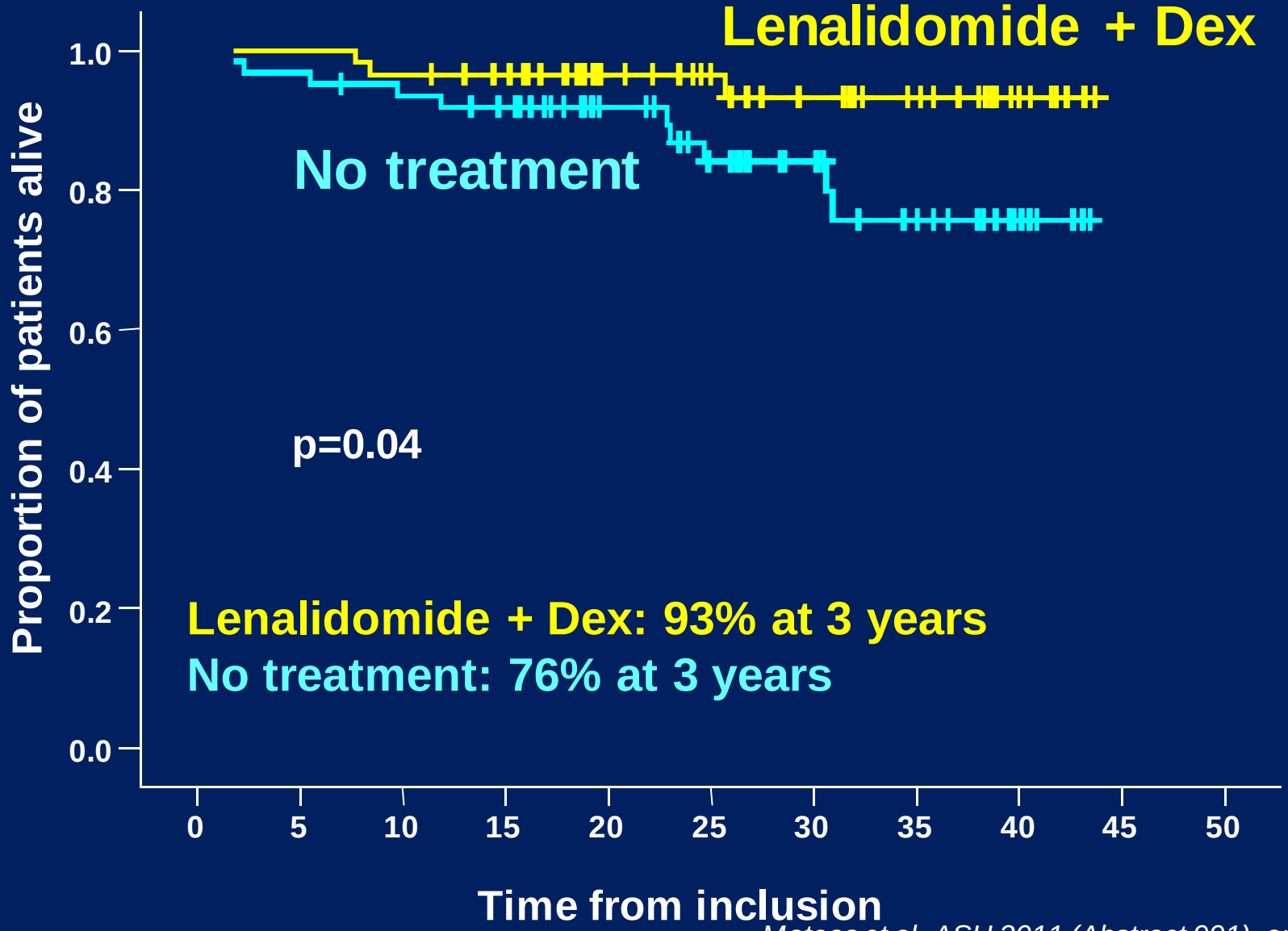
Median follow-up: 32 months (range 12–49)



Mateos et al. ASH 2011 (Abstract 991), oral presentation

Len-dex vs no treatment: OS from inclusion (n = 119)

Median follow-up: 32 months (range 12–49)



Mateos et al. ASH 2011 (Abstract 991), oral presentation

Toxicity profile

During induction (n:57)

	G1-2	G3
Anemia	15 (28%)	1(2%)
Neutropenia	11 (20%)	3 (5%)
Thrombocytopenia	7 (13%)	1 (2%)
Asthenia	11 (20%)	4 (7%)
Constipation	10 (18%)	-
Diarrhea	13 (24%)	1 (2%)
Rash	18 (33%)	2 (4%)
Parestesias	3 (5%)	-
Tremor	7 (13%)	-
Infection*	25 (46%)	4 (6%)
DVT**	3 (5%)	

**One infection was Grade 4*

During maintenance (n:50)

	G1	G2
Anemia	4(11%)	1 (3%)
Neutropenia	1 (3%)	3 (9%)
Thrombocytopenia	-	3 (9%)
Asthenia		1(2%)
Parestesias		1(2%)
Tremor	1(2%)	
Infection	6 (21%)	3 (11%)

***DVT prophylaxis with Aspirin (100mg) in 1 pt, oral anticoagulation in 1 pt with low INR levels and no px in the other one*

Mateos et al. ASH 2011 (Abstract 991), oral presentation

Conclusions/Recommendations

- In clinical trials “high-risk disease” should be defined in a uniform way across trials
- This probably requires combination(s) of clinical and molecular characteristics
- FISH in a standardized way should become mandatory for reports of clinical trials

- It is recommended to include PET-CT (or MRI ?) at start and at end of planned treatment to detect focal lesions and biopsy active lesions
- Molecular profiling in clinical trials may be the next step towards identifying risk groups

Treatment at relapse: sequencing, retreatment and rescue strategies, including update on new agents

Sequence of therapy in MM: Does it matter?

- Retrospective evaluation of patients (n=208) with MM who received bortezomib followed by lenalidomide or vice versa

	Lenalidomide first (n=97)	Bortezomib first (n=111)	p
Median OS	78.5 months	74 months	0.62
Median OS in pts with serum creatinine ≥2 mg/dl at diagnosis	24.1 months	53.9 months	0.01
≥ PR to bortezomib-based therapy	68.%	77.2%	0.265
≥ PR to lenalidomide-based therapy	60.4%	73.6%	0.168

- Multivariable analysis:
  - baseline renal dysfunction and presence of bone disease at diagnosis predictors of worse outcomes
  - sequence of therapy not a predictor of outcome

Patel et al. ASH 2011 (Abstract 3979), poster presentation

VANTAGE 088: Phase 3 Bortezomib + vorinostat vs bortezomib

- Patients (n=637), median age 61 (≥ 65 years 37%)
  - 1-3 prior lines (20% prior bortezomib)
- Treatment (21-day cycles)
  - Bortezomib 1.3 mg/m^2 days 1, 4, 8, 11 +/- vorinostat 400 mg/d days 1 to 14
- Results

	Bortezomib + Vorinostat	Bortezomib	p
ORR	56%	41%	< 0.0001
Median PFS	7.63 months	6.83 months	0.01
Median OS	Not reached	28.1 months	Ns

Dimopoulos et al. ASH 2011 (Abstract 811), oral presentation

VANTAGE 088: Phase 3 Bortezomib + vorinostat vs bortezomib

	Bortezomib + Vorinostat	Bortezomib + placebo
Grade 3/4 hematological adverse events		
Anemia	17%	13%
Thrombocytopenia	45%	24%
Neutropenia	28%	25%
Grade 3/4 non-hematological adverse events		
Constipation	2%	1%
Diarrhea	17%	9%
Nausea	8%	4%
Vomiting	7%	4%
PN	8%	8%
Vorinostat/placebo dose reduction	50%	25%
Discontinuations (mainly due to GI AEs & PN)	21%	22%

Dimopoulos et al. ASH 2011 (Abstract 811), oral presentation

Phase 2: Siltuximab + dex in relapsed/refractory MM

Final results

- Patients (n=49), median age 65 yrs,
  - heavily pretreated (prior bortezomib, steroids, IMiDs, alkylating agents, ASCT)

- Results
  - PR 17%, ≥ MR 23.4
    - Responses in pts refractory to last Dex-containing regimen
  - Median PFS 3.7 months
  - Median OS 20.4 months

  - Non-hematologic grade ≥3 AEs: fatigue (8%), abnormal hepatic function (8%), pneumonia (6%)
  - Grade 4 hematologic toxicities: thrombocytopenia (12%), neutropenia (4%) anemia (2%)
  - 25% of pts discontinued treatment due to an AE

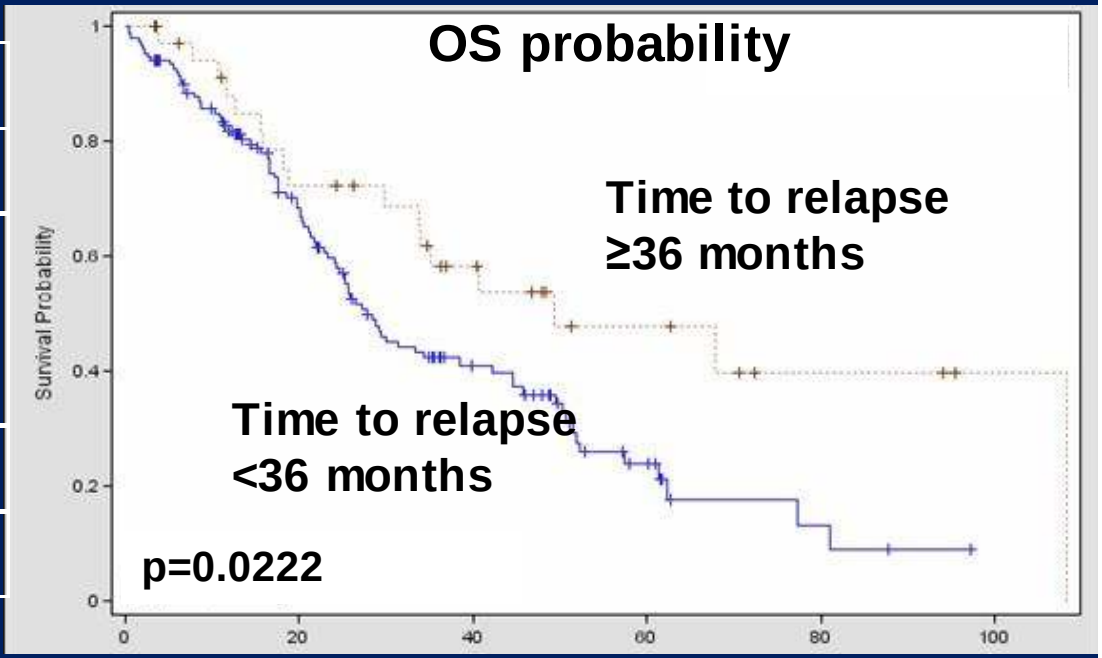
Vorhees et al. ASH 2011 (Abstract 3971), poster presentation

Second ASCT at relapse after prior ASCT

Report From the Center for International Blood and Marrow Transplant Research (CIBMTR)

- n=187
- Median time between ASCT 1 & 2: 32 months (in 69% > 24 months)
- Median follow up after ASCT 2: 47 months

	Post ASCT 2		
	1 year	2 years	3 years
Cumulative incidence of relapse	51%	82%	91%
PFS	47%	13%	5%
OS	83%	46%	29%



- Second ASCT at relapse is feasible
- Best outcome observed in later relapses (>36 months from ASCT 1)

Saad et al. ASH 2011 (Abstract 504), oral presentation

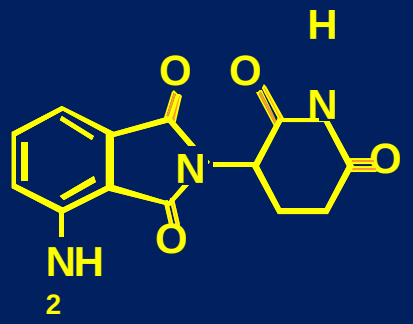
Refractory MM: combinations with bortezomib

Study details	Results	Abstract
Phase 2b trial: Vorinostat + bortezomib in bortezomib-refractory pts (Vantage 095)	n=143 •≥ PR 17%, ≥ MR 31%, ≥ SD 77% •Median OS 11.2 months •Grade 3/4 AEs: Anemia 38%, thrombocytopenia 68%, neutropenia 32%, febrile neutropenia 4%, nausea 7%, diarrhea 17%, fatigue 13% •PN: all grades 22%, gr 3/4 2%	Siegel, ASH 2011, # 480
Phase 2 study: Panobinostat + bortezomib + dex in bortezomib-refractory pts (PANORAMA 2)	n=55 •≥ PR 29%, nCR 4%, PR 25% •≥ MR 49% •Grade 3/4 AEs : thrombocytopenia 53%, anemia 16%, fatigue 16%, diarrhea 14% •PN all grades 24%, 1 grade 3 event	Richardson, ASH 2011, # 814

Refractory MM: combinations with bortezomib

Study details	Results				Abstract
Phase 1/2: Perifosine + Bortezomib -/+ Dex in bortezomib-refractory pts	• n=84				Richardson ASH 2011, # 815
		Response	PFS	OS	
	All pts	≥ PR 22% CR/nCR 4%	6.4 months	25 months	
	Pts refractory to bortezomib	≥ PR 13% CR/nCR 2%	5.7 months	22.5 months	
	• Grade 3/4 AEs: thrombocytopenia 23%, neutropenia 15%, anemia14% • 2 pts with gr 3 PN • No grade 4 PN				

Pomalidomide in Myeloma



Hideshima et al. Blood 96: 2943, 2000
Davies et al. Blood 98: 210, 2001
Gupta et al. Leukemia 15: 1950, 2001

Mitsiades et al. Blood 99: 4525, 2002
Lentzsch et al Cancer Res 62: 2300, 2002
LeBlanc R et al. Blood 103: 1787, 2004
Hayashi T et al. Brit J Hematol 128: 192, 2005

Refractory MM: combinations with IMiDs

Study details	Results	Abstract
Phase 2: Pomalidomide + Dex	• n=84 • No cross-resistance between pomalidomide and lenalidomide	Leleu, ASH 2011, # 812

	ORR	PFS
All pts	34.5%	9.1 months
Pts refractory to len	36%	5.7 months
Pts refractory to len and bortezomib	31%	3.8 months

Phase 2: single agent carfilzomib (PX-171-004)

- **Patients** (n=129), bortezomib-naïve, 65% refractory to most recent therapy

- **Carfilzomib dose**
  - Cohort 1: 20 mg/m^2 for all treatment cycles
  - Cohort 2: dose-escalating regimen of 20 mg/m^2 for cycle 1 and 27 mg/m^2 thereafter

Vij et al. ASH 2011 (Abstract 813), oral presentation

Phase 2: single agent carfilzomib (PX-171-004)

	Cohort 1 (n=59)	Cohort 2 (n=70)
≥ PR	42%	52%
≥ MR	59%	64%
DOR	13.1 months	NR
Time to response	1 month	1.9 months
TTP	8.3 months	NR
PFS	8.2 months	NR
Median OS	NR	NR
PN		
grade 1/2	14%	19%
grade 3/4	2%	0

NR, not reached

PN single-agent bortezomib:

- **Rel/ref MM (APEX) all grades 36%, grade 3/4 8%**

Richardson et al. N Engl J Med **2005**;352(24):2487-98

Vij et al. ASH 2011 (Abstract 813), oral presentation

Marizomib and MLN9708

Study details	Results	Abstract
Phase 1: Marizomib +/- Dex	• 21 pts; bi-weekly • All pts: ≥ SD 55%, MR+PR 15% • Pts refractory to bortezomib: ≥ SD 67%, MR+PR 17% • Pts refractory to len: ≥ SD 62%, MR+PR 23% • AEs: fatigue, nausea, vomiting, headache, fever, dizziness • Dose-limting toxicity: hallucinations • PN, thrombocytopenia, neutropenia not seen	Richardson, ASH 2011, # 302
Phase 1: MLN9708	• 56 pts; biweekly dosing, no dex • ≥PR 6 pts, CR 1 pt, MR 1 pt, SD 28 pts • Grade 3/4 AEs: thrombocytopenia, (n=19), neutropenia (n=8), fatigue (n=5), rash (n=5), abdominal pain, anemia, hypophosphatemia, leukopenia (n=2 for each) • 6 pts (11%) with drug-related PN: 4 gr 1, 2 gr 2	Richardson, ASH 2011, # 301

Phase 2: Elotuzumab + Len + low-dose Dex in relapsed/refractory MM

- Patients (n=73),1-3 prios lines of therapy
- Treatment: Elotuzumab 10 mg/kg or 20 mg/kg + Len + Dex
- Results
  - Response:
    - ORR 82%, ≥ VGPR 36%, sCR/CR 12%
      - 100% ≥ PR in pts with 1 prior therapy
    - Median time to response: 1 month (2 months to best response)
  - Median FU: 14.1 months, median PFS not reached (PFS rate 75%)
  - AEs
    - Grade 3/4 AEs: lymphopenia (16%), thrombocytopenia (16%), neutropenia (16%)
    - Infusion reactions: nausea, pyrexia, rash
      - No Grade 4 infusion reactions
      - Premedication decreased incidence and severity of infusion reactions

Lonial et al. ASH 2011 (Abstract 303), oral presentation

Phase 1: BT062 in rel/ref MM

- **Chimeric humanized IgG4 anti-CD138 mAb**
  - **Covalently linked to tubulin toxin (maytansinoid)**

Results

- **Patients (n=32), median 7 lines prior therapy**
  - **All exposed to bortezomib + IMiDs**
- **Dosing: once every 3 weeks**
- **MTD: 160 mg/m^2**
- **AE:**
  - **Mainly grade 1/2: diarrhea, nausea, fatigue**
  - **Most grade 3/4 AEs due to decrease in blood counts**
  - **SAEs: GI bleed, mucositis, hand-foot syndrome, blurred vision, dray eyes, stomatitis**
- **≥ SD 50%**
- **2 MR, 1 PR**

Jagannath et al. ASH 2011 (Abstract 305), oral presentation

Questions ?