5 Minute JournalClub

Key ASH Presentations

Issue 1, 2011

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CME Information

LEARNING OBJECTIVES

- Identify patients with MM who have undergone autologous stem cell transplant and would benefit from maintenance lenalidomide.
- Counsel older patients (age 65 or older) with MM who have received up-front melphalan/prednisone/lenalidomide about the safety and efficacy of maintenance lenalidomide.
- Counsel patients with MM who are being considered for proteasome inhibitor-based therapy about the safety and efficacy of carfilzomib-based therapy and the possibility of participation in ongoing clinical trials with this novel agent.
- Consider the safety and efficacy of weekly bortezomib maintenance therapy after initial up-front therapy for elderly patients with newly diagnosed MM.
- Counsel appropriately selected elderly patients with MM about the safety and efficacy of up-front bortezomib/melphalan/prednisone/thalidomide (VMPT) followed by maintenance therapy with bortezomib/thalidomide (VT).
- In patients for whom up-front lenalidomide/dexamethasone is being considered, use a lower dose of dexamethasone, which has equivalent efficacy but improved safety compared to higher-dose dexamethasone, regardless of patient age.

CME Information (Continued)

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FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Consulting Agreements: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genzyme Corporation, Medtronic Inc, Otsuka Pharmaceutical Co Ltd; *Paid Research:* Celgene Corporation, Onyx Pharmaceuticals Inc.

Carfilzomib, Lenalidomide, and Dexamethasone In Newly Diagnosed Multiple Myeloma: Initial Results of Phase I/II MMRC Trial

Jakubowiak AJ et al.

Proc ASH 2010;Abstract 862.

Introduction

- Carfilzomib (Cfz) is a novel, irreversible proteasome inhibitor that has demonstrated promising single-agent activity and a favorable toxicity profile, including very low rates of peripheral neuropathy and neutropenia in relapsed/ refractory multiple myeloma (MM) (*Proc ASH* 2010;Abstract 1938).
- Additive anti-MM effects have been reported with carfilzomib in combination with lenalidomide and dexamethasone (CRd) in preclinical studies.
  - Lack of overlapping toxicity allows for the use of these agents at full doses and for extended duration of time in relapsed/refractory MM (*Proc ASH* 2009;Abstract 304).
- **Current Study Goals:** To determine the maximum tolerated dose (MTD) of CRd and to assess safety and evaluate efficacy of this combination in newly diagnosed MM.

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Methods

- **Phase I Carfilzomib Dose Escalation Trial**
- Carfilzomib (C) as only dose-escalating agent (IV on days 1, 2, 8, 9, 15, 16 in 28-day cycles)
  - Level 1: 20 mg/m^2
  - Level 2: 27 mg/m^2 (initial maximal planned dose)
  - Level -1: 15 mg/m^2 (if needed)
  - Level 3: 36 mg/m^2 (study amendment inclusion after toxicity assessment
- Lenalidomide (Len, R) administered at 25 mg PO (days 1-21) for all dose levels
- Dexamethasone (Dex, d) administered at 40/20 mg PO weekly (cycles 1-4/5-8) for all dose levels

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Methods (continued)

- **Phase I/II (Target Accrual = 36)**
- Patients achieving ≥ partial response (PR) proceed to stem cell collection (SCC) and autologous stem cell transplant (ASCT) after ≥ 4 cycles.
  - ASCT candidates offered continued CRd treatment after SCC
- After completion of 8 cycles, patients receive 28-day maintenance cycles
  - C (days 1, 2, 15, 16), R days 1-21, and d weekly at the doses tolerated at the end of 8 cycles
- 24 patients have been enrolled to date:
  - Level 1 (C, 20 mg/m^2) – 4 patients
  - Level 2 (C, 27 mg/m^2) – 14 patients
  - Level 3 (C, 36 mg/m^2) – 6 patients

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Response Rates by IMWG*

Clinical Response	CRd (n = 19)
≥Partial response (PR)	100%
≥Very good partial response	63%
Complete response (CR)/near CR	37%

* Response in evaluable patients (pts) who completed at least 1 cycle after a median of 4 (range 1-8) months of treatment

- Responses were rapid with 17 pts achieving PR after 1 cycle and improving responses with continuing therapy in all pts.
- 7 pts proceeded to SCC after a median of 4 cycles of CRd (range 4-8); all resumed CRd treatment after SCC.
- After a median of 4 months of follow-up, all evaluable pts are alive without disease progression.

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Adverse Events (AE)

Hematologic	CRd (n = 21)
Neutropenia (Grade 3 or 4)	14%
Thrombocytopenia (Grade 3 or 4)	14%
Anemia (Grade 3)	10%
Nonhematologic (Grade 3)	
Peripheral neuropathy (PN) (Grade 3 or 4)*	0%
Fatigue	5%
Mood alteration†	5%
Glucose elevations†	24%
Deep vein thrombosis (while receiving aspirin prophylaxis)	5%

* Only 2 cases of Grade 1 PN were reported, even after prolonged treatment
† AE related to dexamethasone administration

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Conclusions

- Carfilzomib plus lenalidomide/dexamethasone (CRd) is well tolerated and highly active in newly diagnosed MM.
  - ≥PR = 100%
  - ≥VGPR = 63%
  - CR/nCR = 37%
- These data represent the first report to date of treatment of front-line myeloma with carfilzomib and add support to the Phase III trial of CRd versus Rd in relapsed MM (NCT01080391).

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Investigator comment on the Phase I/II trial of carfilzomib, lenalidomide and dexamethasone in newly diagnosed multiple myeloma

This study is addressing the role of carfilzomib as an alternative to bortezomib as induction therapy for myeloma. Carfilzomib has activity in myeloma and has lesser neuropathic potential than bortezomib, and the combination presented in this paper is similar to the lenalidomide, bortezomib and dexamethasone (RVD) regimen, previously reported by Dr Richardson.

This study was received with great enthusiasm, as the response rate was essentially 100 percent with many complete responses and VGPRs. The regimen will have to be tested in larger Phase II/III trials. Examining these results, it does appear that carfilzomib, in combination with other agents, has enough antitumor activity to make it a serious contender against any regimen that is based on proteasome inhibition, and it appears to be safe for patients.

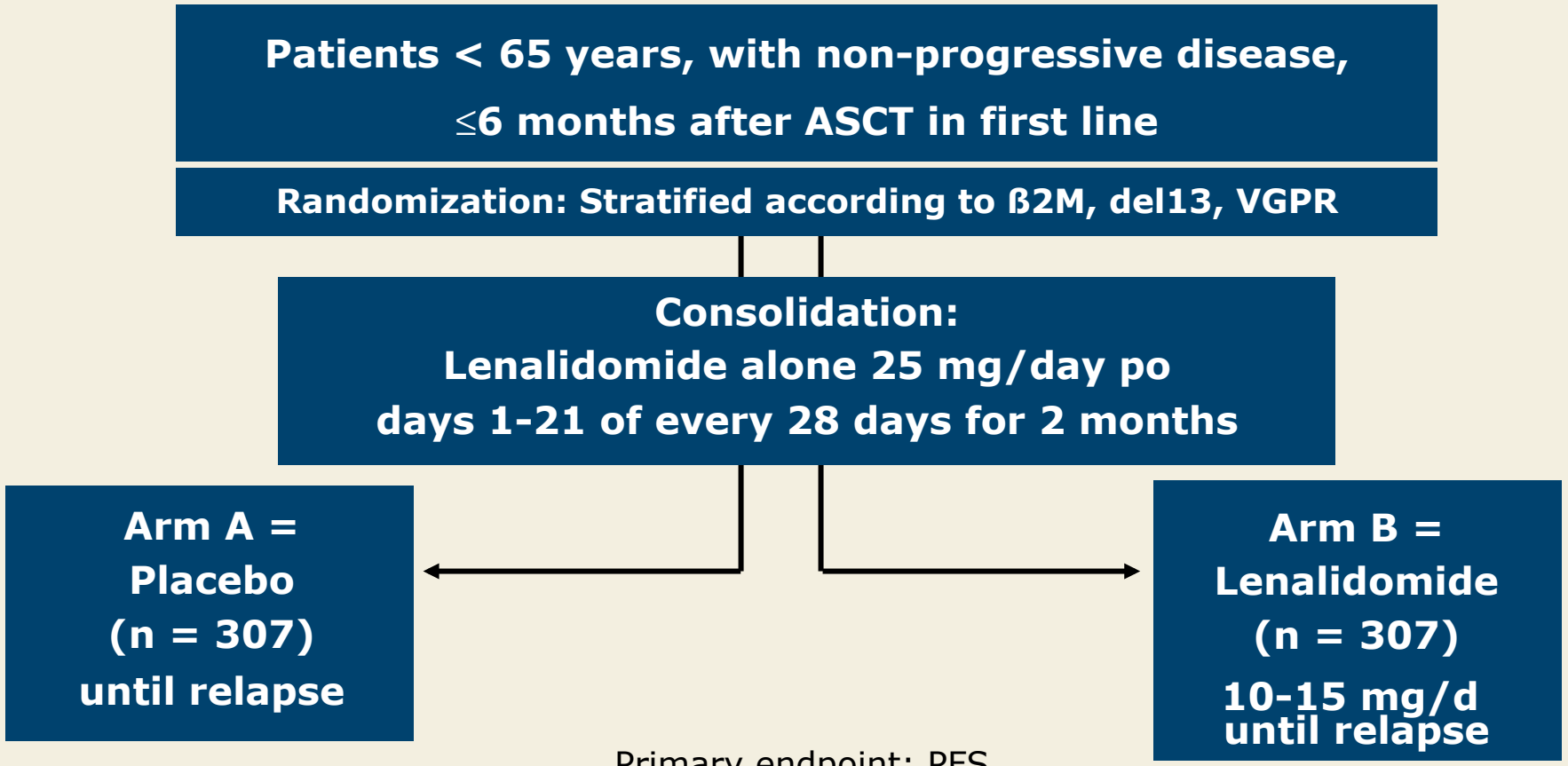
Interview with Rafael Fonseca, MD, December 22, 2010

Maintenance Treatment with Lenalidomide After Transplantation for MYELOMA: Final Analysis of the IFM 2005-02

Attal M et al.

Proc ASH 2010;Abstract 310.

IFM 2005-02 Study Schema



Primary endpoint: PFS

Secondary endpoints: CR rate, TTP, OS, feasibility of long-term lenalidomide

Attal M et al. *Proc ASH* 2010;Abstract 310; Attal M et al. *Proc ASCO* 2010;Abstract 8018.

Post-Randomization Progression-Free Survival (PFS)

	Arm A	Arm B	Hazard ratio	*p*-value
Progression or death[2]	47%	25%	—	—
Median PFS from randomization*[1]	24 mos	42 mos	0.50	$<10^{-8}$
3-year post-randomization PFS[2]	34%	68%	—	—

* Median follow-up: 34 months

[1] Attal M et al. *Proc ASH* 2010;Abstract 310; [2] Attal M et al. *Proc ASCO* 2010;Abstract 8018.

Conclusions

- Lenalidomide maintenance improved PFS versus placebo following ASCT in patients with newly diagnosed MM.
  - Median PFS: 42 months vs 24 months ($p < 10^{-8}$)
  - Benefit was observed across all stratified subgroups of patients (data not shown)
  - PFS was related to lenalidomide maintenance ($p < 0.0001$) and achievement of CR/VGPR after consolidation ($p < 0.01$) in multivariate analysis (data not shown)
- Lenalidomide maintenance was well tolerated (data not shown).
  - Definitive interruption rate for serious adverse events during maintenance was similar in both arms (Arm A = 5%, Arm B = 8%)
- These data demonstrate that lenalidomide is an effective and well tolerated maintenance treatment after transplantation for patients with newly diagnosed MM.

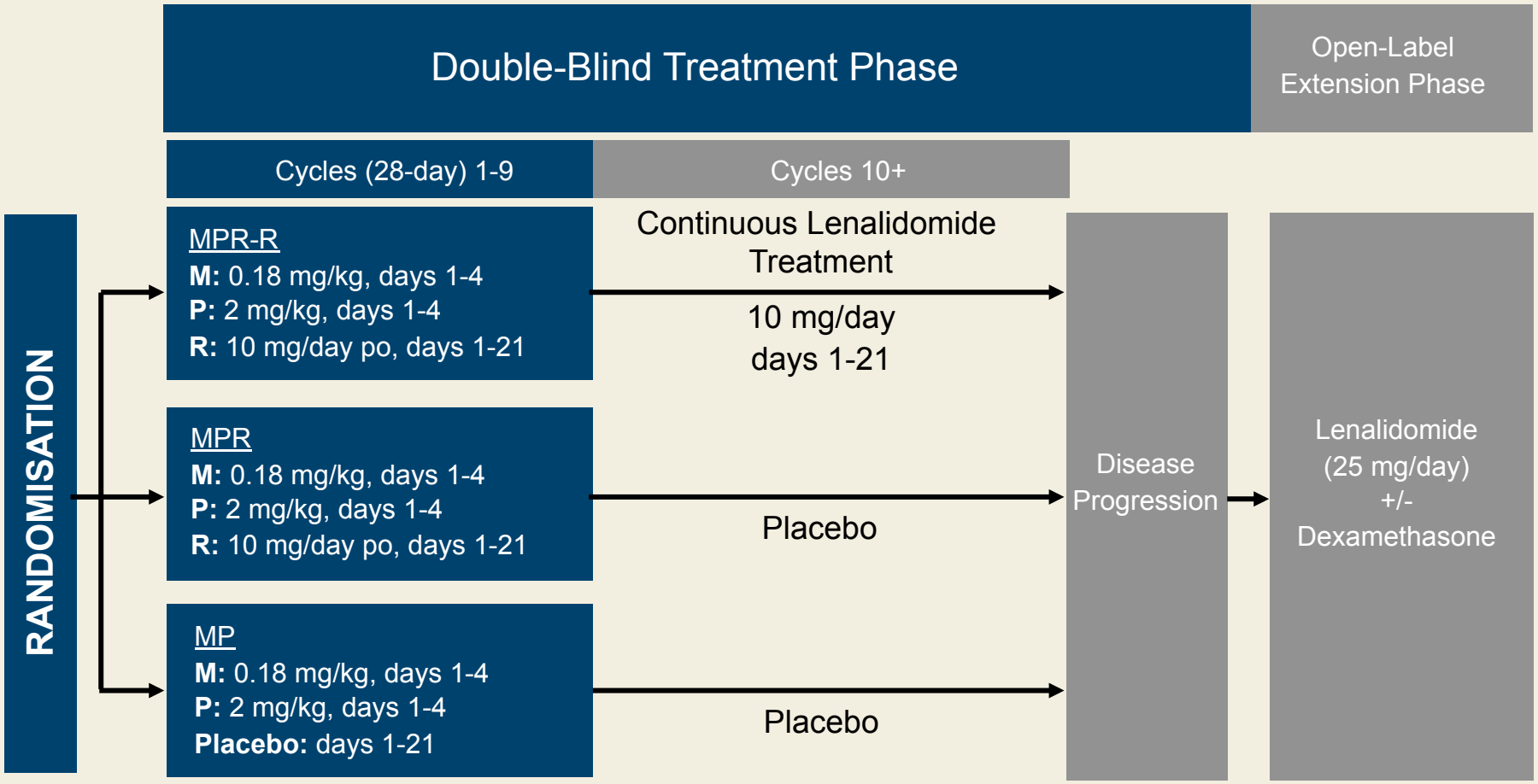
Attal M et al. *Proc ASH* 2010;Abstract 310.

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

Palumbo A et al.

Proc ASH 2010;Abstract 622.

Phase III Study Schema

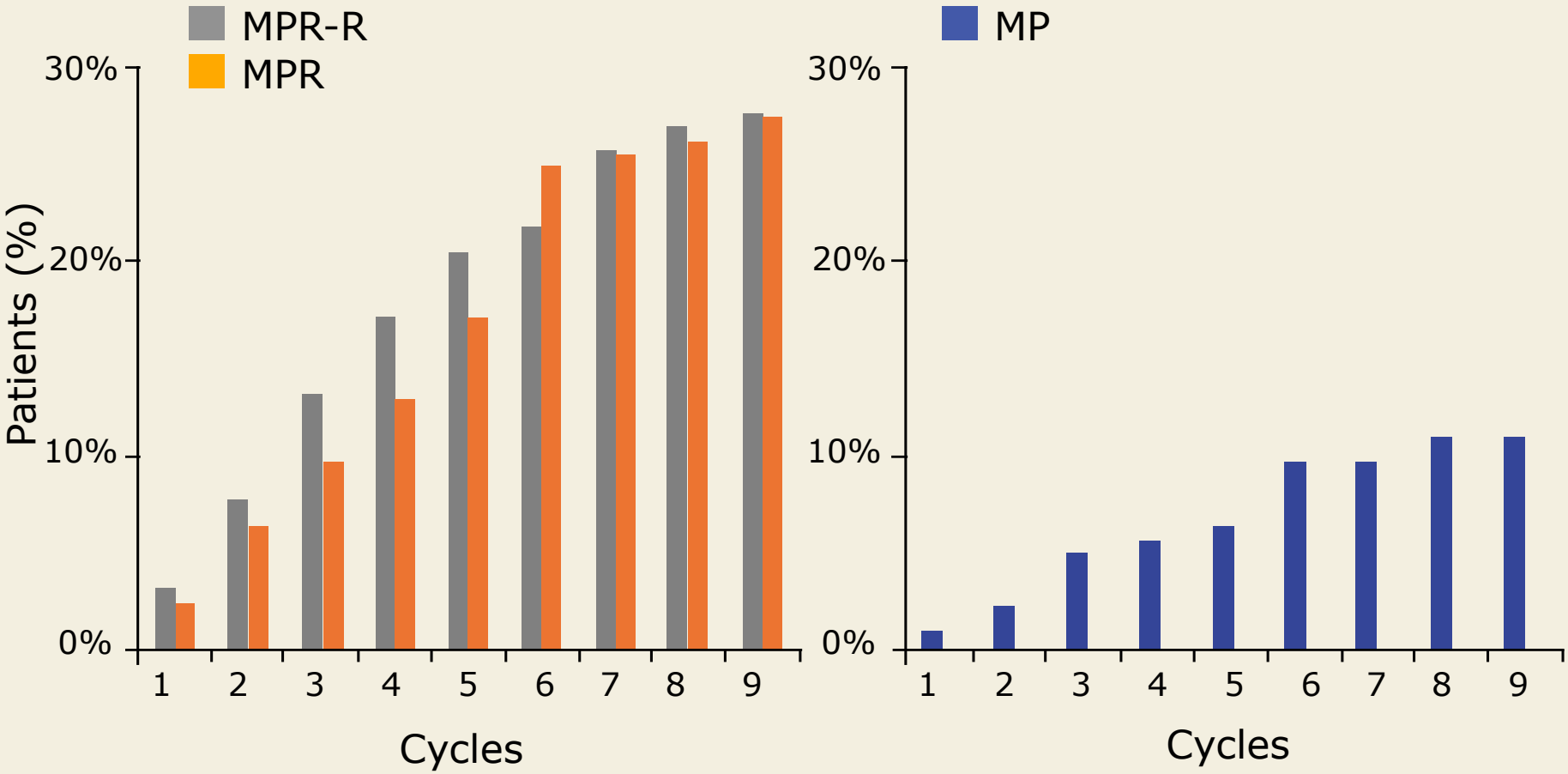


Stratified by age (≤75 vs >75 years) and stage (ISS I/II vs III)

M = melphalan; P = prednisone; R = lenalidomide

Palumbo A et al. *Proc ASH* 2010;Abstract 622.

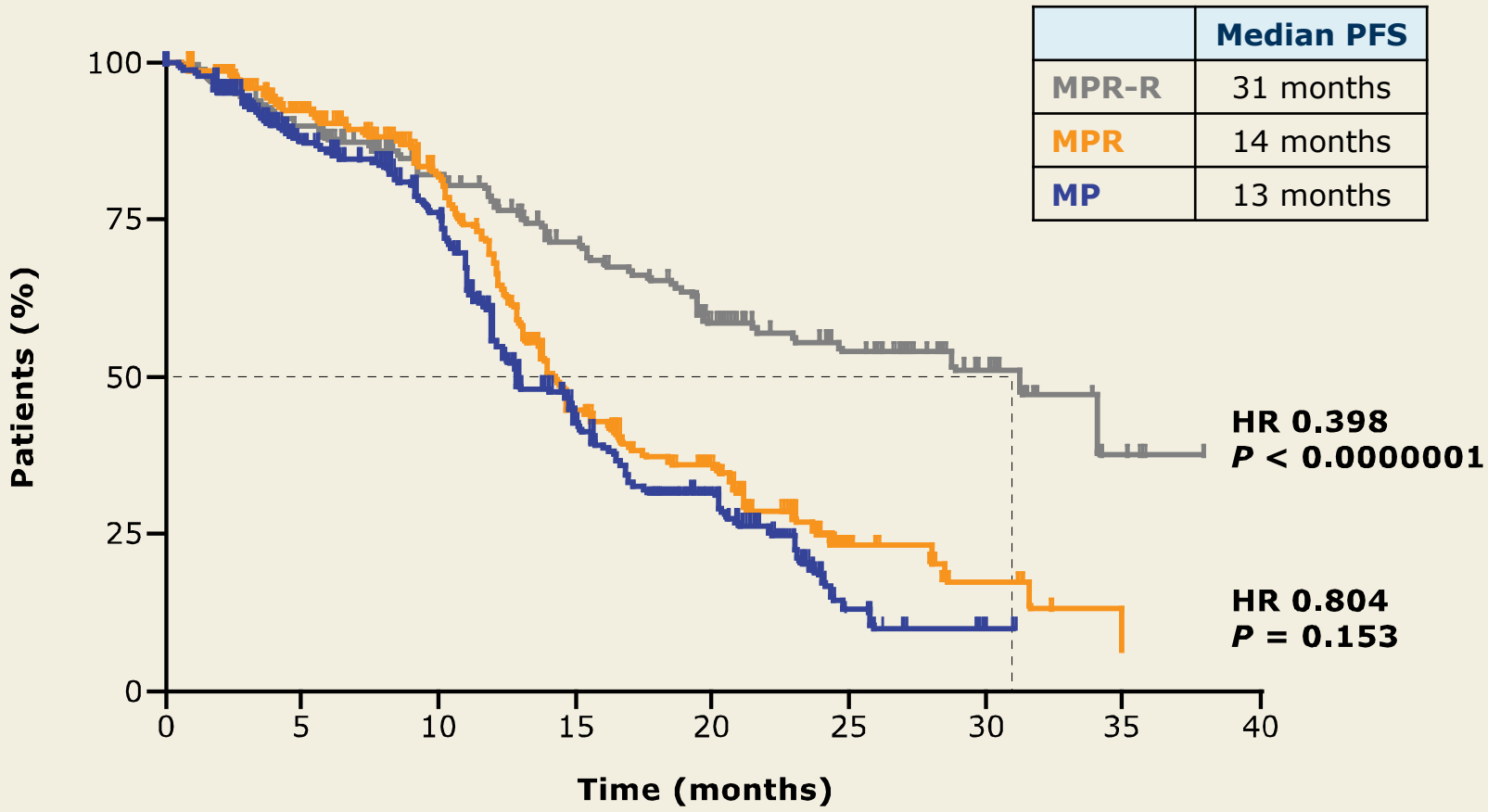
Response Rate



All patients achieved very good response rate or better.

With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Progression-Free Survival (PFS)*
All Patients



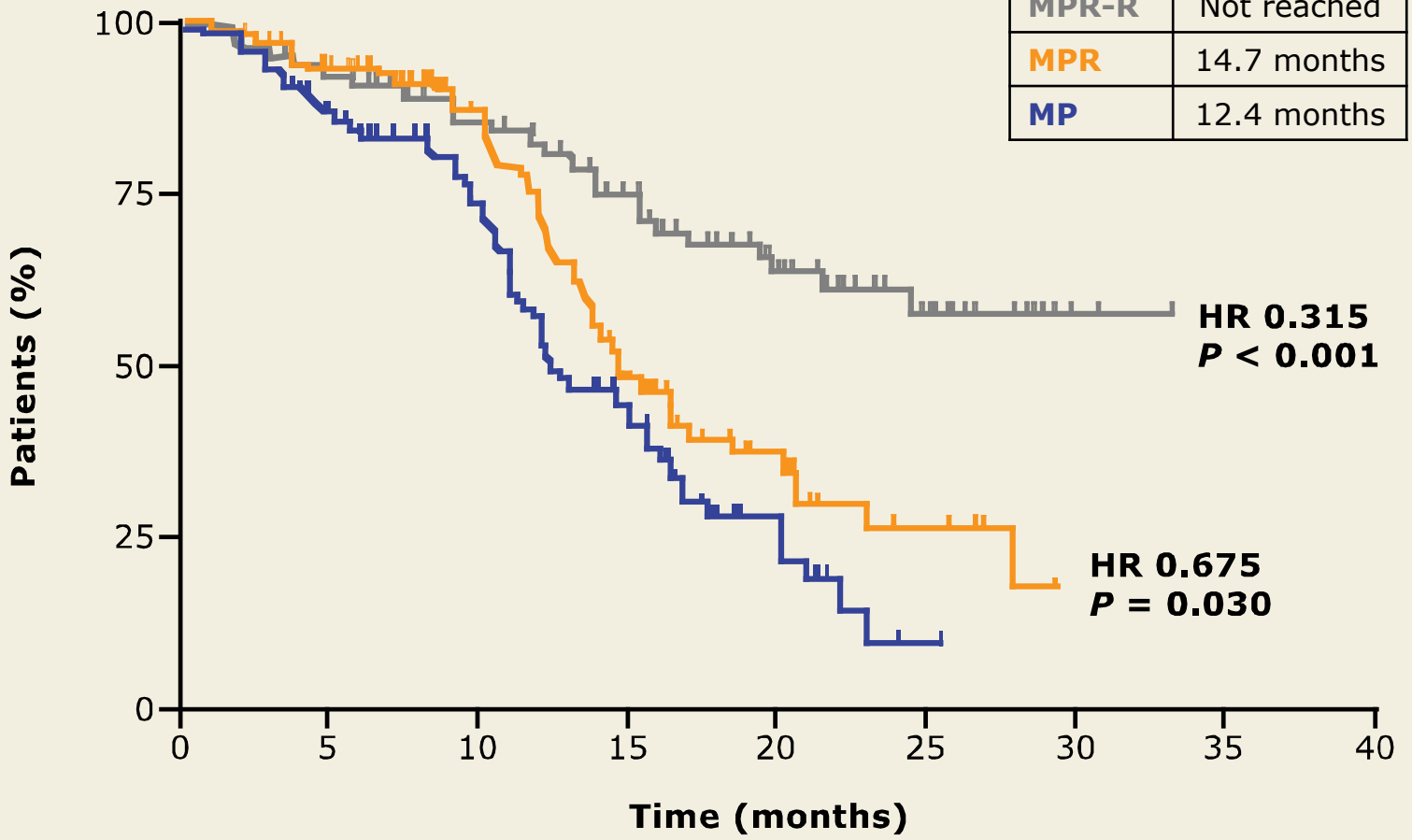
Median follow-up 25 months

* Analysis based on data up to May 2010

With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Progression-Free Survival (PFS) Patients Age 65-75 Years

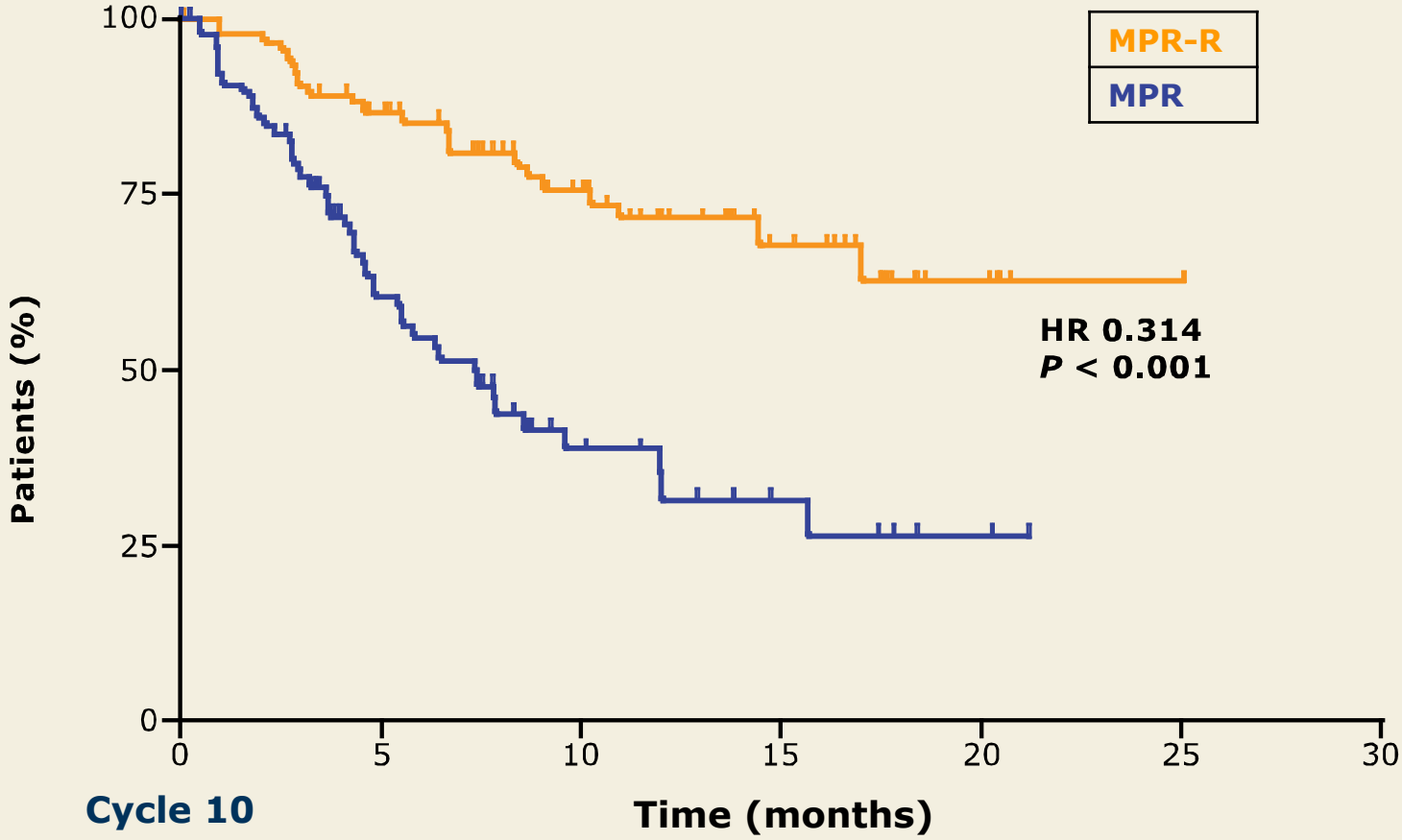
	Median PFS
MPR-R	Not reached
MPR	14.7 months
MP	12.4 months



With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Landmark Analysis

MPR | **Lenalidomide Continuous Therapy**



With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Select Adverse Events During Induction and Maintenance

Hematologic (Grade 4)	MPR-R (n = 150)	MPR (n = 152)	MP (n = 153)
Anemia	5%	3%	1%
Febrile neutropenia	2%	1%	0
Neutropenia	36%	32%	8%
Thrombocytopenia	13%	14%	4%
Non-hematologic (Grade 3 or 4)	**MPR-R**	**MPR**	**MP**
Infections	11%	15%	9%
Pulmonary embolism	2%	2%	0
Deep vein thrombosis	3%	5%	<1%
Fatigue	6%	2%	3%
Rash	5%	5%	<1%
Solid tumors	<1%	3%	1%

Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Conclusions

- Patients receiving MPR-R for NDMM achieved a higher ORR, as well as better quality and more rapid responses vs MP.
- MPR-R compared with fixed-duration regimens of MP and MPR resulted in an unprecedented reduction in the risk of progression with a manageable safety profile, and similar rates of progressive disease.
  - Median PFS: 31 months ($p < 0.0000001$)
  - Greatest benefit reported in patients age 65–75
- Continuous lenalidomide therapy with MPR-R may be superior to regimens of limited duration by providing sustained disease control in transplant-ineligible patients with NDMM.

Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Investigator comment on lenalidomide maintenance for patients with myeloma

The study results updated by Dr Attal continued to show significant improvement in PFS with lenalidomide maintenance post-transplantation. The overall survival (OS) results are not mature yet, but I presume that with additional follow-up, this study will ultimately show an improvement in OS as the majority of studies with thalidomide maintenance have shown improvement in OS. However, lenalidomide is both more effective and less toxic than thalidomide. I believe most physicians are discussing these results with patients so that an informed decision can be made by the eligible patient.

The MPR regimen is active, although during the first few months after treatment initiation no clear distinction can be seen among the three arms. I believe the MPR combination does have a significant risk of myelosuppression, and I would not recommend MPR for induction in an off-study setting. The important take-home message from this study is that a significant prolongation of PFS is present in the arm which had the lenalidomide maintenance.

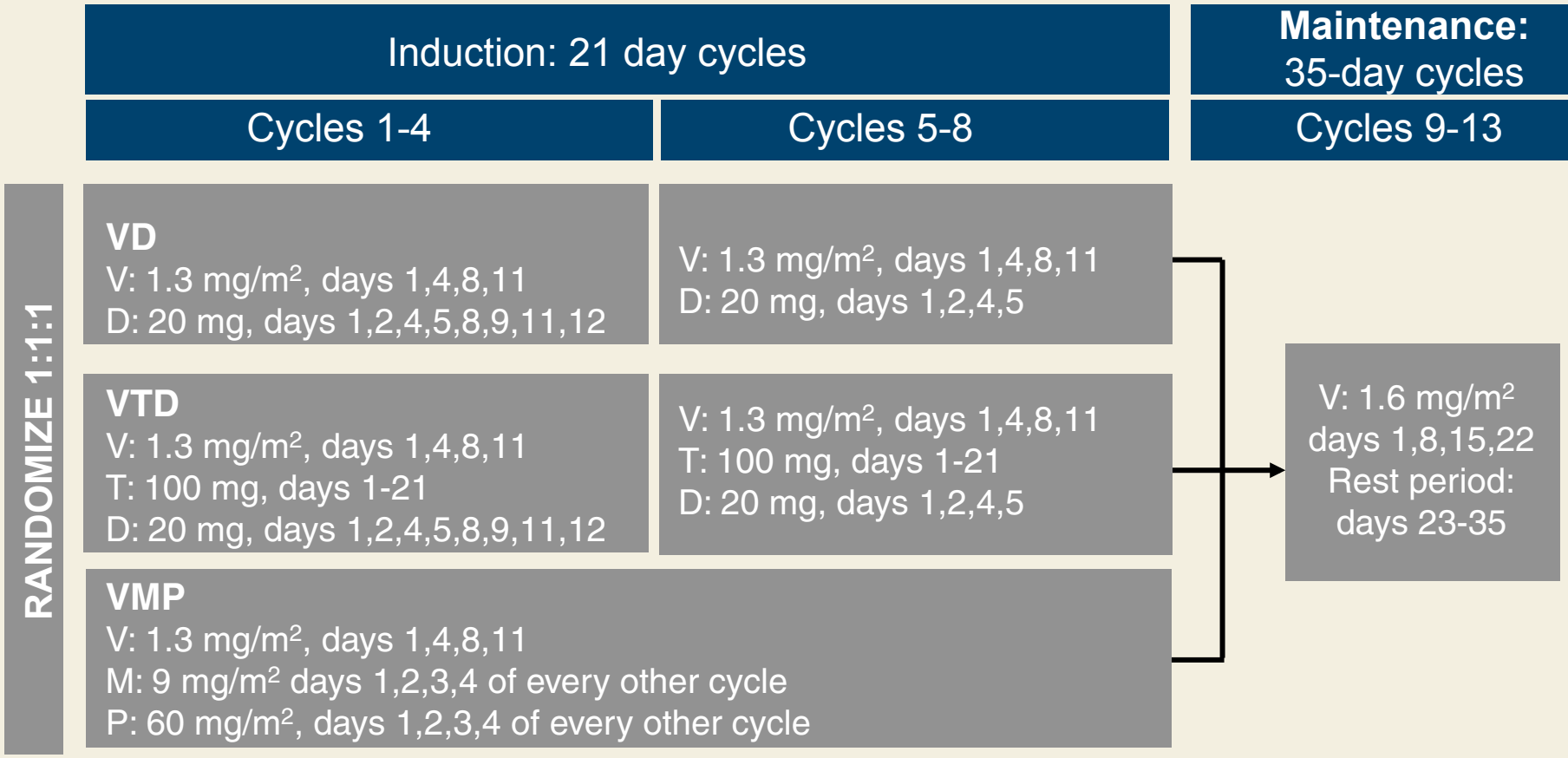
Interview with Rafael Fonseca, MD, December 22, 2010

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

Niesvizky R et al.

Proc ASH 2010;Abstract 619.

UPFRONT Study Schema



D = dexamethasone; M = melphalan; P = prednisone; T = thalidomide; V = bortezomib

Niesvizky R et al. *Proc ASH* 2010;Abstract 619.

Efficacy Endpoints

	VD (n = 167)	VTD (n = 168)	VMP (n = 167)
Median PFS	13.8 mos	18.4 mos	17.3 mos

Response rates after induction therapy (I) and after V maintenance (M)

	VD		VTD		VMP	
	I	**M**	**I**	**M**	**I**	**M**
ORR	68%	71%	78%	79%	71%	73%
CR + nCR	24%	31%	36%	38%	31%	34%
≥VGPR	36%	39%	44%	47%	40%	44%

CR = complete response; nCR = near CR; ORR = overall response rate;
PFS = progression-free survival; VGPR = very good partial response

Niesvizky R et al. *Proc ASH* 2010;Abstract 619.

Select Grade ≥3 Adverse Events (AE)

	VD		VTD		VMP	
	I (n = 99)	M (n = 55)	I (n = 93)	M (n = 31)	I (n = 99)	M (n = 43)
Peripheral neuropathy (PN)	15%	5%	26%	6%	20%	2%
Grade ≥3 PN resulting in discontinuation of all study drugs	4%	4%	13%	0%	14%	0%
Fatigue	8%	4%	15%	0%	8%	0%
Neutropenia	1%	0%	3%	0%	21%	0%
Diarrhea	8%	5%	4%	3%	7%	7%
Pneumonia	11%	0%	6%	0%	4%	5%

Niesvizky R et al. *Proc ASH* 2010;Abstract 619.

Conclusions

- All three regimens were active in the treatment of elderly patients with newly diagnosed multiple myeloma.
  - Grade ≥3 AEs, serious AEs, PN and study discontinuations due to AEs were highest in the VTD arm.
- Single-agent bortezomib maintenance therapy post induction resulted in some increase of ≥VGPR rates in all three arms and was well tolerated.
  - Compared to post-induction rates, the rates of all-grade and Grade ≥3 PN did not increase substantially in any of the three treatment arms.
- PFS appeared similar between the treatment arms in the intent-to-treat population.

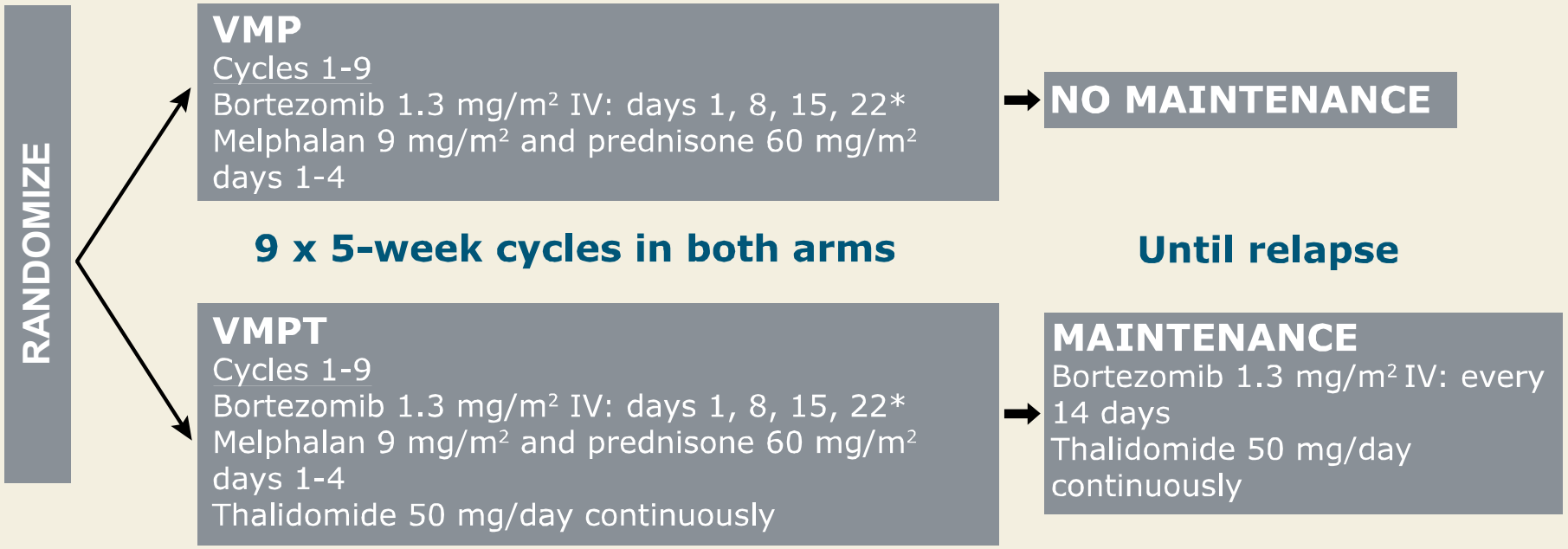
Niesvizky R et al. *Proc ASH* 2010;Abstract 619.

Bortezomib, Melphalan, Prednisone and Thalidomide Followed by Maintenance with Bortezomib and Thalidomide (VMPT-VT) for Initial Treatment of Elderly Multiple Myeloma Patients: Updated Follow-Up and Impact of Prognostic Factors

Palumbo A et al.

Proc ASH 2010;Abstract 620.

Study Schema

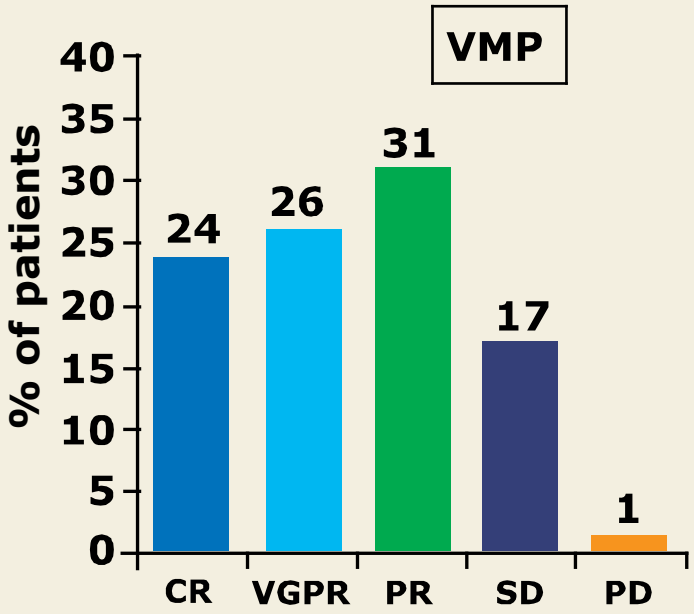


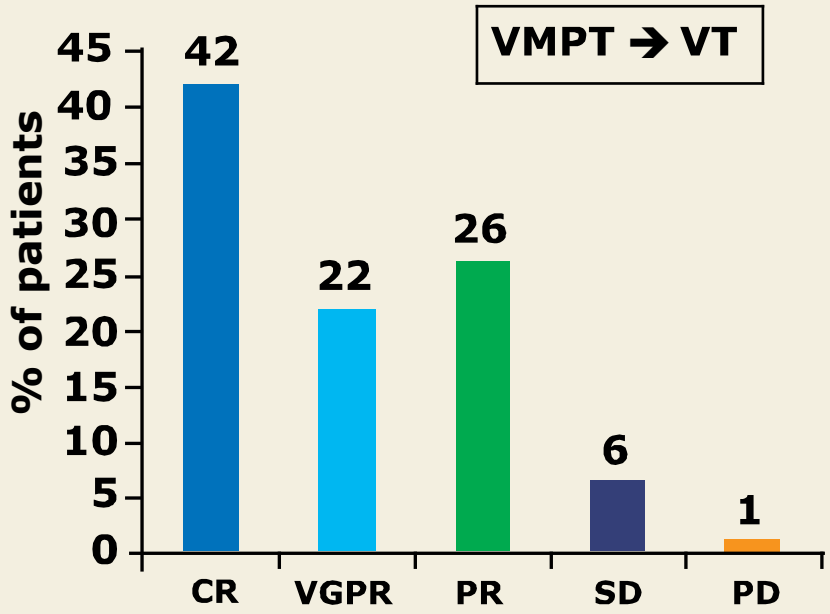
* 66 VMP patients and 73 VMPT patients were treated with twice weekly infusions of bortezomib

Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Best Response Rates

	VMP (N = 253)	VMPT-VT (N = 250)	*p*-value
CR	24%	42%	<0.0001
≥VGPR	50%	64%	0.001
≥PR	81%	90%	0.007





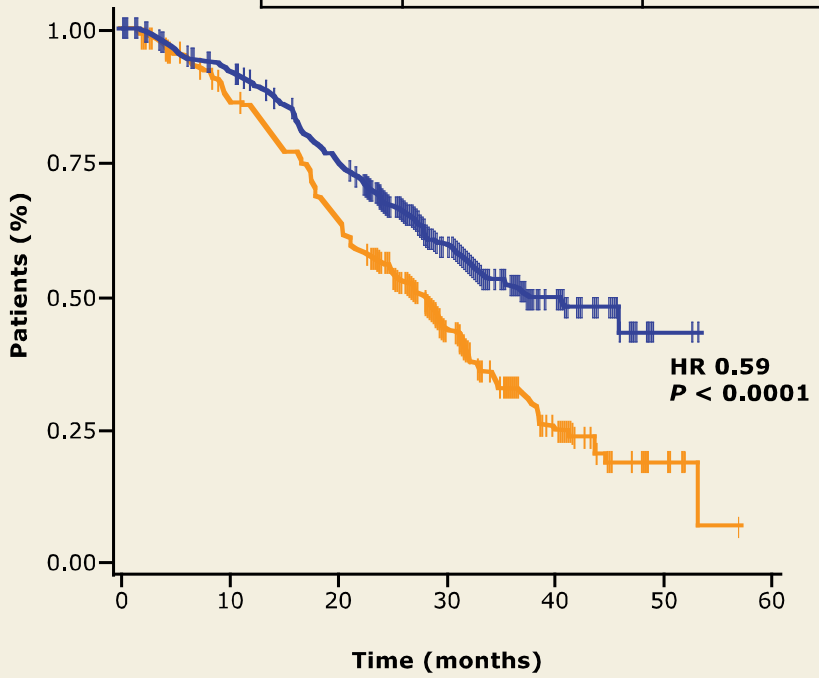
With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Results: Progression-Free Survival and Time to Next Therapy

Progression-Free Survival

41% Reduced Risk of Progression

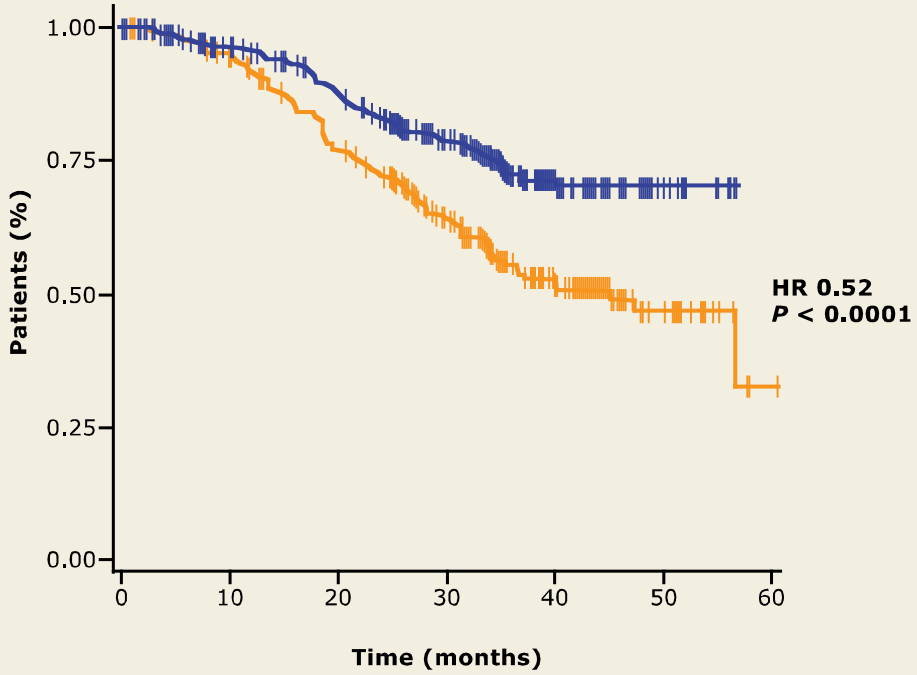
	3-years PFS	Median PFS
VMPT	51%	37.2 months
VMP	32%	27.4 months



Time to Next Therapy

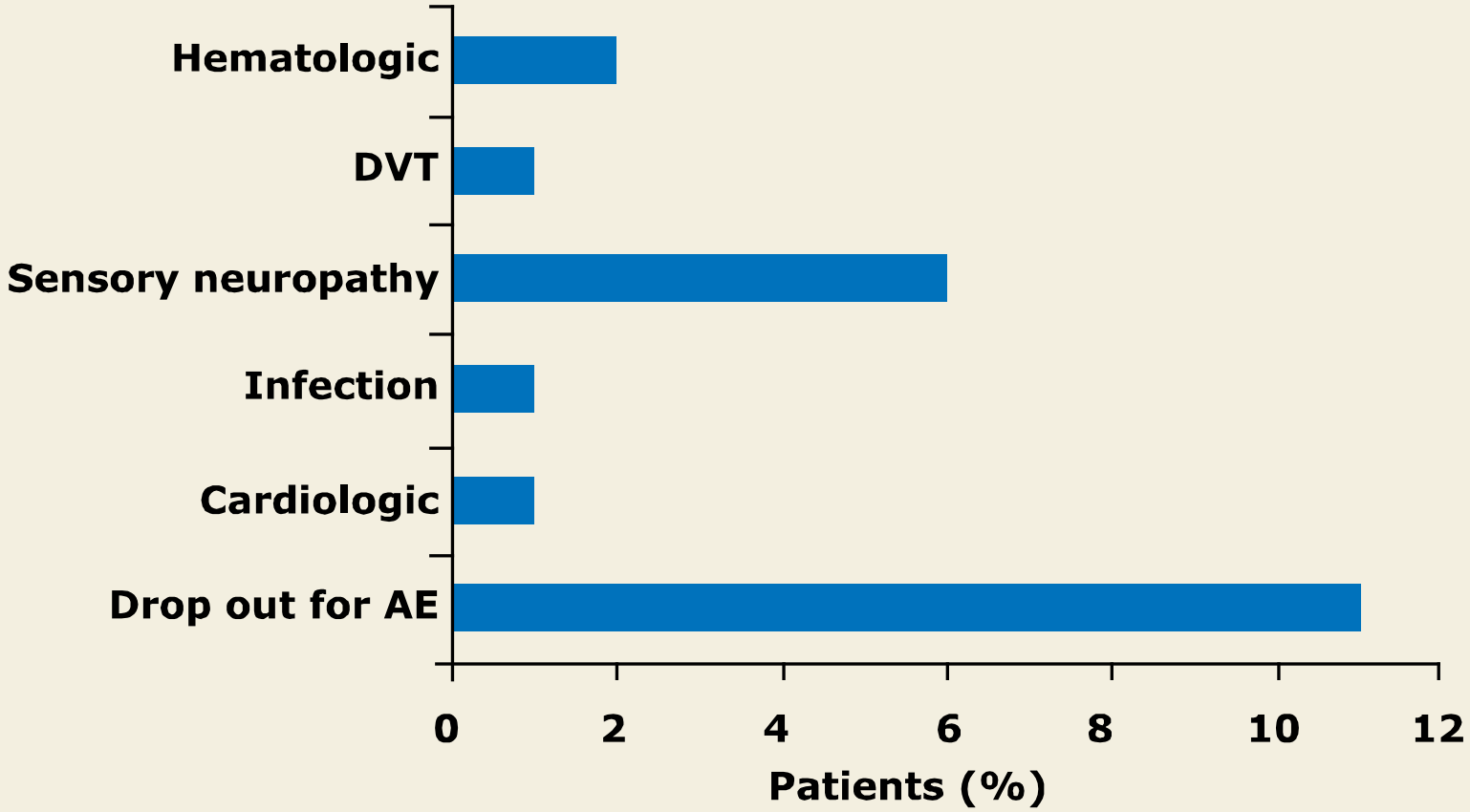
48% R

	3-years TNT	Median TTNT
VMPT	70%	Not reached
VMP	51%	37.6 months



With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 620.

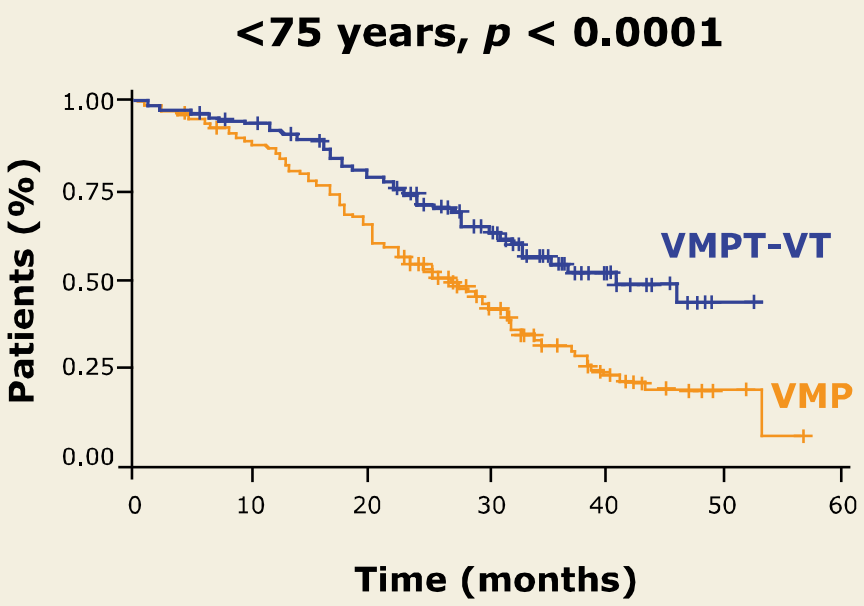
Grade 3 or 4 Adverse Events After Cycle 9 (Maintenance Phase)

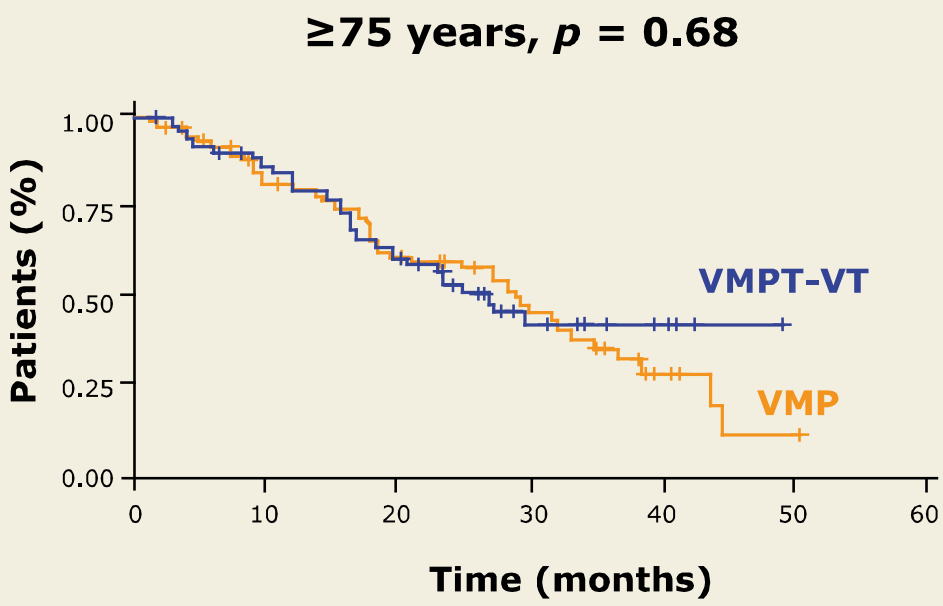


Newly occurring or worsening Grade 3 or 4 adverse events

With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 620.

PFS According to Age





With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Conclusions

- Statistically significant improvements reported with VMPT → VT versus VMP for treatment of newly diagnosed MM.
  - CR rate: 42% vs 24% ($p < 0.0001$)
  - Median PFS: 37 months vs 27 months ($p < 0.0001$)
- VMPT → VT prolonged PFS with an unprecedented 3-year PFS of 55% in elderly patients (data not shown).
- Higher dose-intensity regimens seemed to be less effective in frail patients (≥75 years).
- Maintenance therapy with VT further improved PFS with a good safety profile.

Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Investigator comment on bortezomib-based maintenance regimens as part of initial management of myeloma in elderly patients

The UPFRONT study presented by Dr Niesvizky is important because it addressed the role of maintenance therapy for patients who normally would otherwise receive a short duration of treatment. The main point of this paper is that a longer duration of therapy with bortezomib maintenance, after initial induction, improves the response rates and the duration of disease control. For certain patients, such as those with high-risk disease, bortezomib maintenance is not only appropriate but also desirable.

The study presented by Dr Palumbo showed a high degree of activity with VMPT. The postinduction maintenance approach included the combination of two of the most active class of agents: proteasome inhibitors and IMiDs®. In my opinion VMPT is probably not ready for prime time as similar efficacy outcomes from three-drug combinations could also be seen. The maintenance part of the study confirms that the duration of therapy is important in the management of myeloma.

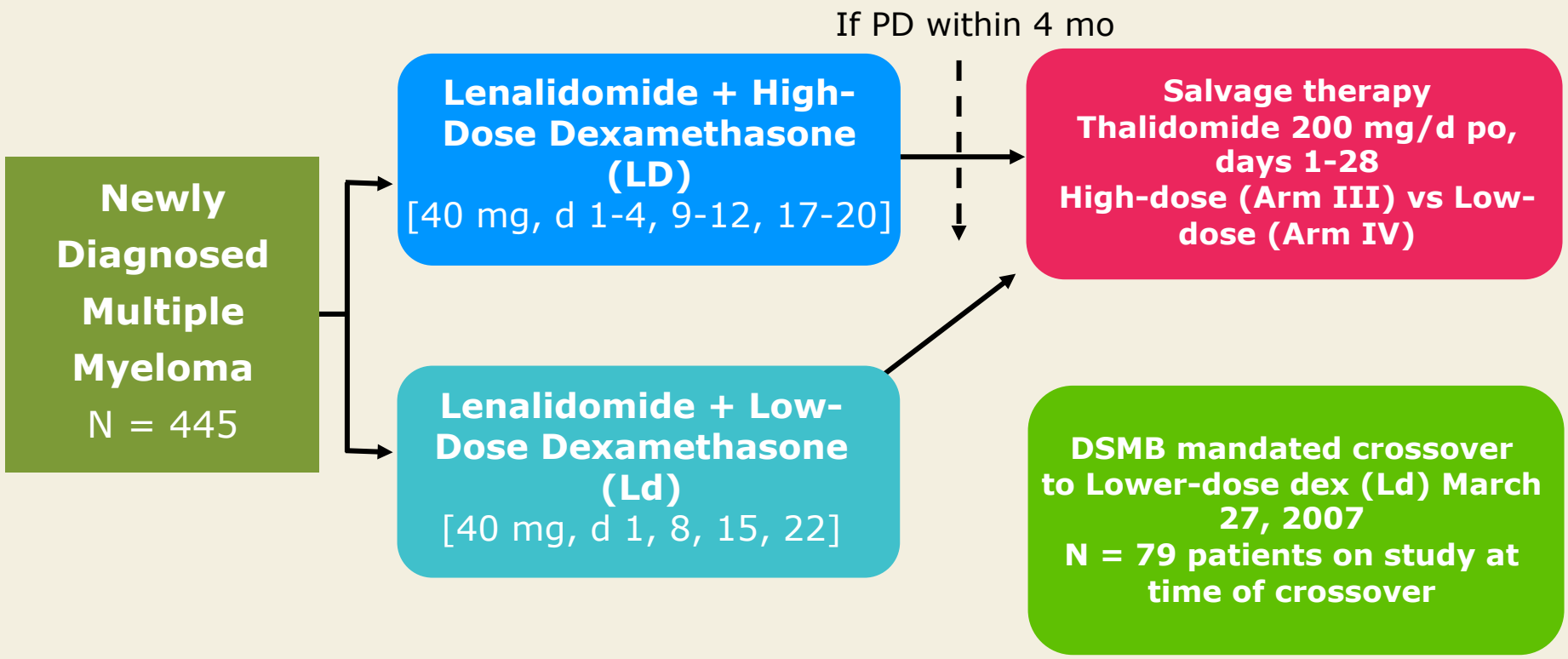
Interview with Rafael Fonseca, MD, December 22, 2010

Lenalidomide plus Low-Dose Dexamethasone (Ld): Superior One and Two Year Survival Regardless of Age Compared to Lenalidomide plus High-Dose Dexamethasone (LD)

Vesole DH et al.

Proc ASH 2010;Abstract 308.

ECOG-E4A03 Study Schema



Lenalidomide: 25 mg daily, days 1-21 of a 28-day cycle; High-dose Dex: total 480 mg/28-day cycle; Low-dose Dex: total 160 mg/28-day cycle

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

Best Response: ≥PR

	LD (n)	Ld (n)	Odds ratio	*p*-value
Overall	81.3% (214)	70.2% (208)	1.85	0.009
<65	85.4% (103)	66.0% (103)	3.02	0.002
≥65	77.5% (111)	74.3% (105)	1.19	0.634
≥70	74.6% (71)	73.8% (65)	1.04	1.000
≥75	77.8% (36)	70.4% (27)	1.47	0.566

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

Overall Survival Probability

Intent-to-Treat Analysis				
	1-year OS		2-year OS	
Age	**Ld**	**LD**	**Ld**	**LD**
< 65 (n = 108; 104)	0.96	0.92	0.92	0.86
> 65 (n = 114; 119)	0.95	0.84	0.85	0.72
> 70 (n = 71; 76)	0.96	0.78	0.89	0.67
> 75 (n = 30; 38)	0.90	0.76	0.76	0.60
4-Month Landmark Analysis				
	1-year OS		2-year OS	
Age	**Ld**	**LD**	**Ld**	**LD**
< 65 (n = 106; 103)	0.98	0.93	0.93	0.86
> 65 (n = 113; 109)	0.96	0.92	0.86	0.79
> 70 (n = 70; 67)	0.97	0.88	0.90	0.76
> 75 (n = 29; 34)	0.93	0.85	0.79	0.67

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

Adverse Events

	≥Grade 3 or 4 nonhematologic toxicity		All Grade 5 toxicity	
	Ld	**LD**	**Ld**	**LD**
Overall	50.5%	61.4%	2.3%	5.8%
Age < 65	45.8%	52.9%	1.0%	1.9%
Age > 65	54.9%	68.9%	3.5%	9.2%
Age ≥ 70	60.6%	68.4%	4.2%	13.2%
Age ≥ 75	66.7%	71.1%	10.0%	13.2%

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

Conclusions

- OS was not superior with LD compared to Ld in any age group despite a higher response rate with LD in patients < 65.
  - Response rate was not significantly improved in any other age group
  - Confirmed in the landmark analysis to eliminate the 5% early deaths seen in the first 4 months of treatment.
- OS benefit with Ld accrues as age increases.
- No age group shows a superior outcome with LD, yet toxicities are higher in all age groups.
- Lenalidomide plus low-dose dexamethasone (Ld) is the treatment of choice for ALL age groups.
- It is unknown if extrapolation of Ld data in up-front setting can be applied to the treatment of relapsed MM.

Vesole DH et al. *Proc ASH* 2010;Abstract 308.

Investigator comment on lenalidomide-based induction and maintenance for patients with myeloma

I was a participant in the study by Dr Vesole. When this study showed globally that Ld was superior to LD, an immediate criticism arose that this would be true for the elderly, but certain individuals, such as younger patients, might be better served by LD.

This presentation basically states that there is no age category in which LD is superior to Ld. However, I would agree that the question is still valid whether certain clinical settings exist in which treatment with high doses of dexamethasone may be considered. One clinical situation in which the high-dose dexamethasone approach might be relevant is in the setting of acute renal failure, with which there is a definite need to control the myeloma as soon as possible. The level of toxicity is clearly higher with higher doses of dexamethasone, and the bulk of the evidence suggests that there is no advantage with its use.

Interview with Rafael Fonseca, MD, December 22, 2010