Lenalidomide, Bortezomib, and Dexamethasone Combination Therapy in Patients with Newly Diagnosed Multiple Myeloma

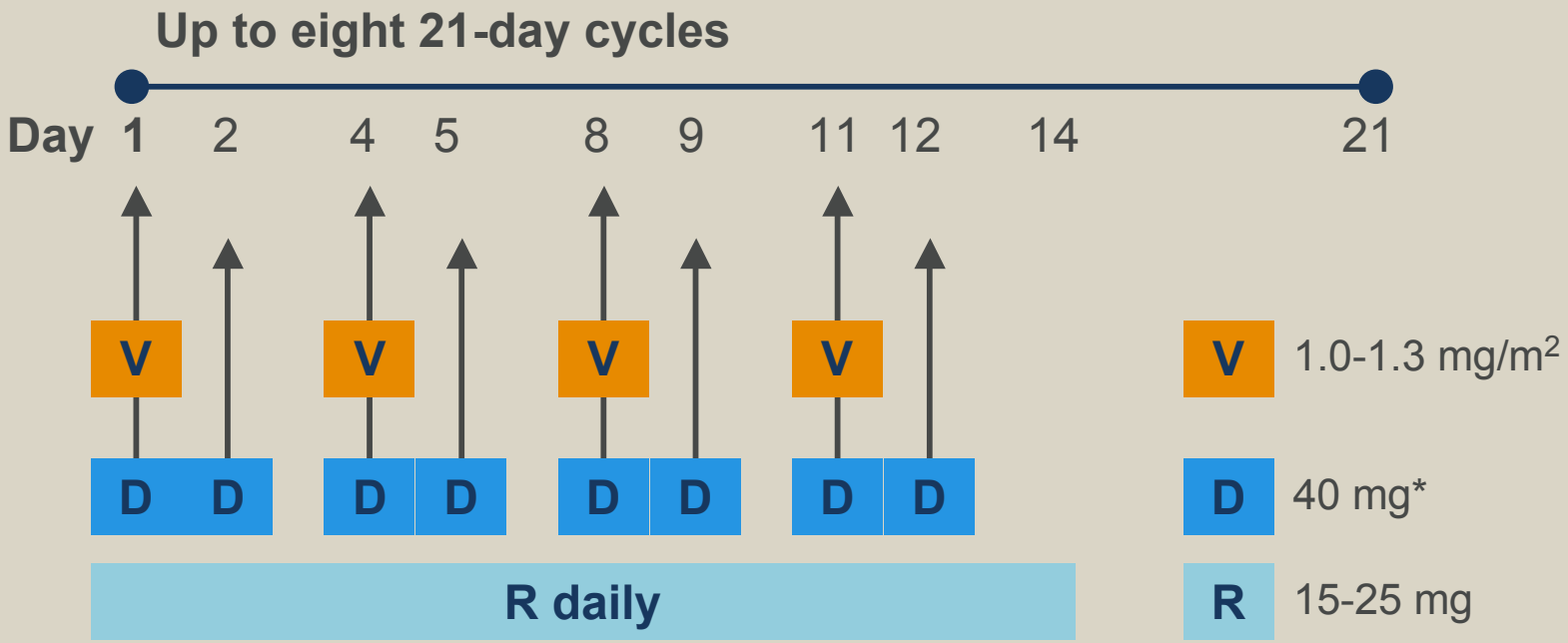
Richardson PG et al.
Blood 2010;116(5):679-86.

Introduction

- Bortezomib (V) is approved for the treatment of multiple myeloma (MM).
- Lenalidomide (R) in combination with dexamethasone (D) is approved for the treatment of relapsed MM after ≥1 prior therapy.
- RV ± D is active and well tolerated in relapsed/refractory MM.
- RD and VD are active in front-line MM.
- Current study goals: To determine the maximum tolerated dose of RVD and to assess safety and efficacy in patients with previously untreated MM.

Richardson PG et al. *Blood* 2010;116(5):679-86.

Study Design: Phase I/II



* Protocol amendment: D dose reduced to 20 mg (cycles 1-4), 10 mg (cycles 5-8)
Maintenance therapy beyond cycle 8 permitted in responding patients

Richardson PG et al. *Blood* 2010;116(5):679-86.

Baseline Characteristics

Characteristic	All patients (n = 66)
Median age	58 years
Male	55%
Myeloma type	
IgG	68%
IgA	23%
Light chain	9%
ISS Stage II/III at diagnosis	56%

Richardson PG et al. *Blood* 2010;116(5):679-86.

Best Response to Treatment

Response	All patients (n = 66)	Phase II population (n = 35)
Complete response (CR)	29%	37%
Near CR (nCR)	11%	20%
Very good partial response (VGPR)	27%	17%
Partial response (PR)	33%	26%
CR + nCR	39%	57%
CR + nCR + VGPR	67%	74%
At least PR	100%	100%

Per EBMT criteria, all response categories, including VGPR, required a confirmatory assessment at 6 weeks.

Richardson PG et al. *Blood* 2010;116(5):679-86.

Select Adverse Events

Nonhematologic	All grades	Grade 3 or 4
Sensory neuropathy	80%	2%
Fatigue	64%	3%
Neuropathic pain	32%	3%
Hematologic		
Lymphopenia	14%	14%
Thrombocytopenia	NR	6%
Neutropenia	NR	9%
Thrombosis	6%	5%

NR = not reported

Richardson PG et al. *Blood* 2010;116(5):679-86.

Author Conclusions

- RVD is a highly effective regimen for previously untreated MM.
  - May represent the basis of future standard treatment in this setting.
- Phase III studies are evaluating VD with or without R (NCT00522392) and RD with or without V (NCT00644228) to assess the benefit of the 3-drug approach.
- An international prospective study is ongoing to assess this combination with or without autologous stem cell transplant, followed by maintenance.

Richardson PG et al. *Blood* 2010;116(5):679-86.

Faculty Comments

DR ZONDER: These are the only data we have at the moment on the use of this triplet regimen as front-line therapy. RVD has an unprecedented response rate. These results establish RVD as the backbone to which future regimens must be compared. It's not a difficult regimen for the average patient, though both of the novel agents can be difficult for individual patients.

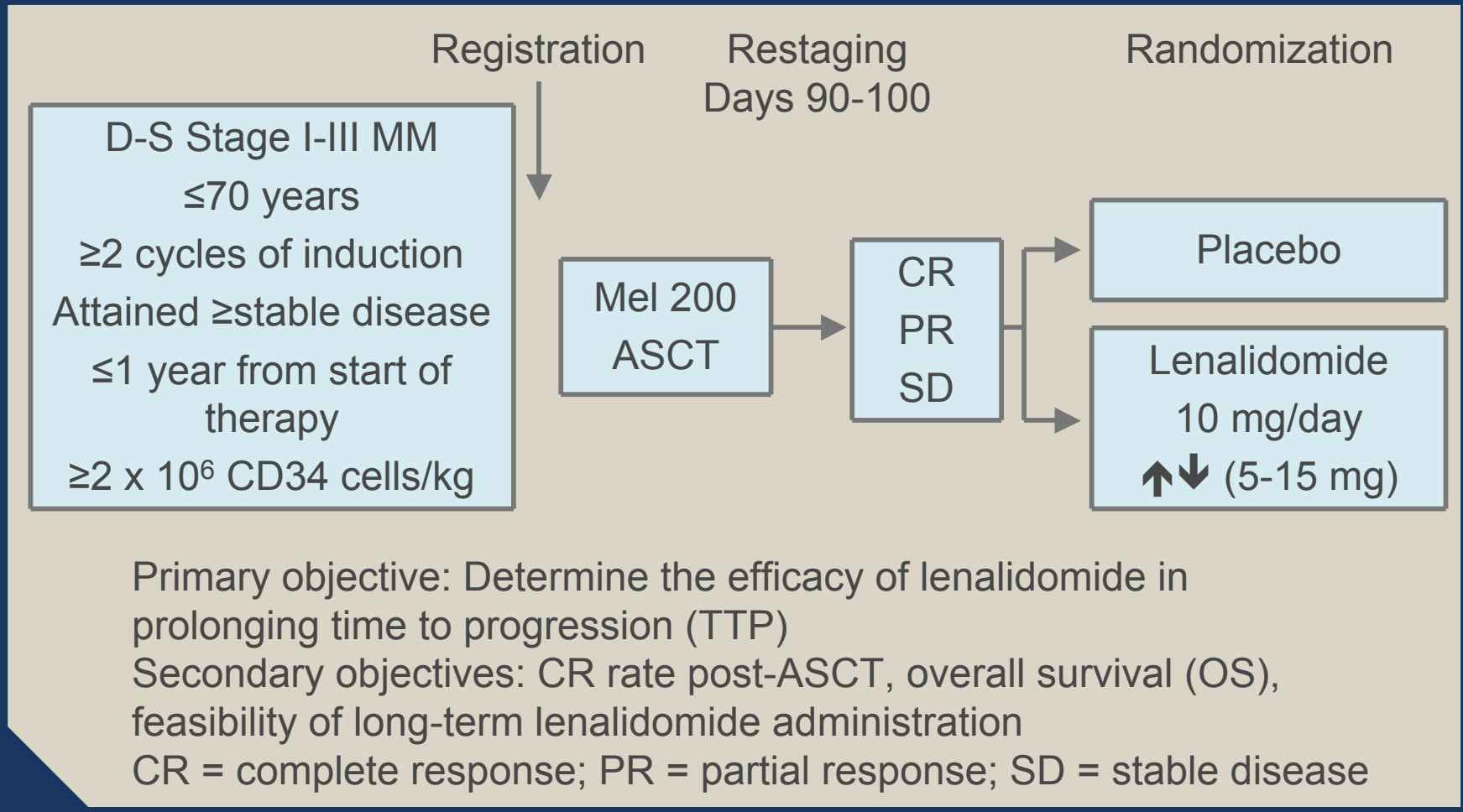
Occasionally, neuropathy is rapid in onset and fairly severe with bortezomib. Lenalidomide can cause deep vein thrombosis, so patients should be monitored accordingly. This regimen deserves to be studied further in randomized trials.

Phase III Intergroup Study of Lenalidomide versus Placebo Maintenance Therapy Following Single Autologous Stem Cell Transplant (ASCT) for Multiple Myeloma (MM): CALGB ECOG BMT-CTN 100104

McCarthy P et al.

Proc International Myeloma Workshop 2011.

CALGB-100104 Study Schema



Primary objective: Determine the efficacy of lenalidomide in prolonging time to progression (TTP)
Secondary objectives: CR rate post-ASCT, overall survival (OS), feasibility of long-term lenalidomide administration
CR = complete response; PR = partial response; SD = stable disease

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Efficacy

	Placebo (n = 229)	Lenalidomide (n = 231)	Hazard ratio	*p*-value
Median TTP	30.9 mo	48.0 mo	0.44	<0.0001
OS (events)	39 deaths	23 deaths	0.51	0.018
Median event-free survival (EFS)	30.9 mo	43.4 mo	0.51	<0.0001

Median follow-up from transplant: 28 months

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Second Cancers: Hematologic

	Placebo (n = 229)	Lenalidomide (n = 231)
Hematologic cancers	0	8
Myelodysplastic syndromes	0	1
Acute myeloid leukemia	0	5
Acute lymphoblastic leukemia	0	1
Hodgkin lymphoma	0	1

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Second Cancers: Solid Tumors

	Placebo (n = 229)	Lenalidomide (n = 231)
Gastrointestinal cancer	0	2
Breast cancer	0	2
Gynecologic cancer	0	2
CNS cancer	0	1
Prostate cancer	0	1
Thyroid cancer	0	1
Melanoma	2	1
Carcinoid tumor	1	0
Sarcoma	1	0

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Author Conclusions

- Maintenance therapy with lenalidomide after single ASCT significantly prolongs TTP versus placebo.
- A statistically significant improvement in OS was seen on the lenalidomide arm of the most recent data analysis (median follow-up of 28 months post-ASCT).
- Second cancers may be increased in patients receiving lenalidomide but without significant effect on EFS or OS (at current analysis).
- Research efforts continue to identify risk factors for the development of second cancers.

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Author Conclusions (continued)

- Lenalidomide prolonged TTP and EFS even after stratification by diagnostic ß2M level and prior thalidomide or lenalidomide induction therapy (data not shown).
- TTP and EFS were superior in patients receiving lenalidomide as part of induction and post-ASCT maintenance or continued therapy.
- After primary therapy, maintenance or continued therapy studies with lenalidomide and other agents, alone or in combination, may determine optimal strategies for long-term MM disease control.

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Faculty Comments

DR BENSINGER: This trial reported a similar higher incidence of second primary cancers to that seen on the French IFM 2005-02 trial. What's different and interesting is that the CALGB study reported a 50% reduction in time to disease progression for patients who received lenalidomide maintenance versus placebo. A statistically significant overall survival benefit was also reported.

This is a potential "game changer" even if more second primary cancers occur with lenalidomide maintenance. If you can show an improvement in survival, then it negates the concern about second primary cancers because there were so few. Still, I don't believe the verdict is in and will await further follow-up on these 2 studies.

Maintenance Treatment with Lenalidomide After Transplantation for Myeloma: Analysis of Secondary Malignancies Within the IFM 2005-02 Trial

Attal M et al.

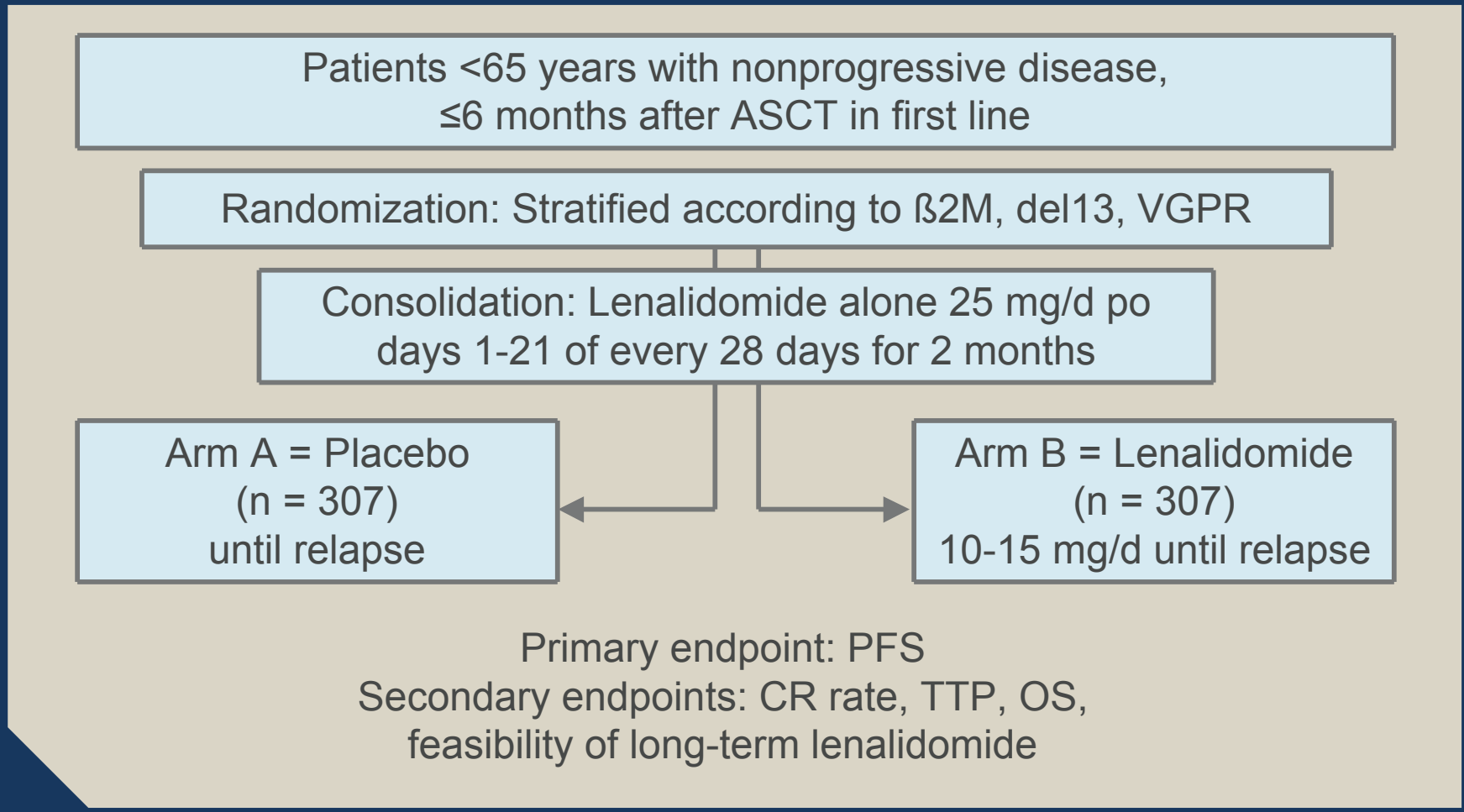
Proc International Myeloma Workshop 2011.

Introduction

- The Phase III IFM 2005-02 trial evaluated the efficacy of lenalidomide maintenance after transplantation for patients with multiple myeloma.
  - Maintenance lenalidomide improved progression-free survival (PFS) and was well tolerated.
  - However, several patients developed secondary hematologic or solid cancers.
- Analyses of secondary cancers reported by all IFM centers for patients on IFM 2005-02 were conducted.

Attal M et al. *Proc International Myeloma Workshop* 2011.

IFM 2005-02 Study Schema



Attal M et al. *Proc International Myeloma Workshop* 2011.

Progression-Free and Overall Survival

	Placebo (n = 307)	Lenalidomide (n = 307)	Hazard ratio	*p*-value
PFS* (months)	24	41	0.5	$<10^{-8}$
5-year OS	73%	79%	1.05	Not significant

* PFS benefit was observed across all stratified patient subgroups.
Median follow-up: 36 months postrandomization, 46 months postdiagnosis
PFS = progression-free survival; OS = overall survival

Attal M et al. *Proc International Myeloma Workshop* 2011.

Second Primary Cancers

	Placebo (n = 302)	Lenalidomide (n = 306)
Hematologic cancers	3	11
AML/MDS	3	5
ALL	0	2
Hodgkin lymphoma	0	4
Solid tumors	3	12

AML = acute myeloid leukemia; MDS = myelodysplastic syndromes;
ALL = acute lymphoblastic leukemia

Attal M et al. *Proc International Myeloma Workshop* 2011.

Author Conclusions

- Maintenance therapy with lenalidomide:
  - Is associated with a low rate of neuropathy and DVT (data not shown)
  - Results in improved PFS compared to placebo: 50% reduction in the risk of disease progression in all stratified subgroups, including response, β2M and FISH
  - Is associated with increased risk of secondary cancers, primarily after 24 months

Attal M et al. *Proc International Myeloma Workshop* 2011.

Author Conclusions (continued)

- Other risk factors for secondary cancers were:
  - Age >55 years
  - Male sex
  - International Staging System Stage III
  - Induction with dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) (data not shown)
- Longer follow-up is needed to determine the effect on OS

Attal M et al. *Proc International Myeloma Workshop* 2011.

Faculty Comments

DR BENSINGER: This trial demonstrated markedly improved progression-free survival for the patients who received lenalidomide. The higher incidence of second cancers is somewhat concerning. These tended to be hematologic cancers, not largely seen in the group who received placebo, so these results raised the issue of prior melphalan exposure and possible second cancers.

DR ZONDER: I believe the increased risk of secondary cancers observed with lenalidomide is outweighed by the antimyeloma benefit that is obtained. The emerging story from the maintenance trials is that longer therapy results in longer disease control. We've known that a risk of secondary cancers exists after anthracycline-containing and alkylator-containing therapy.

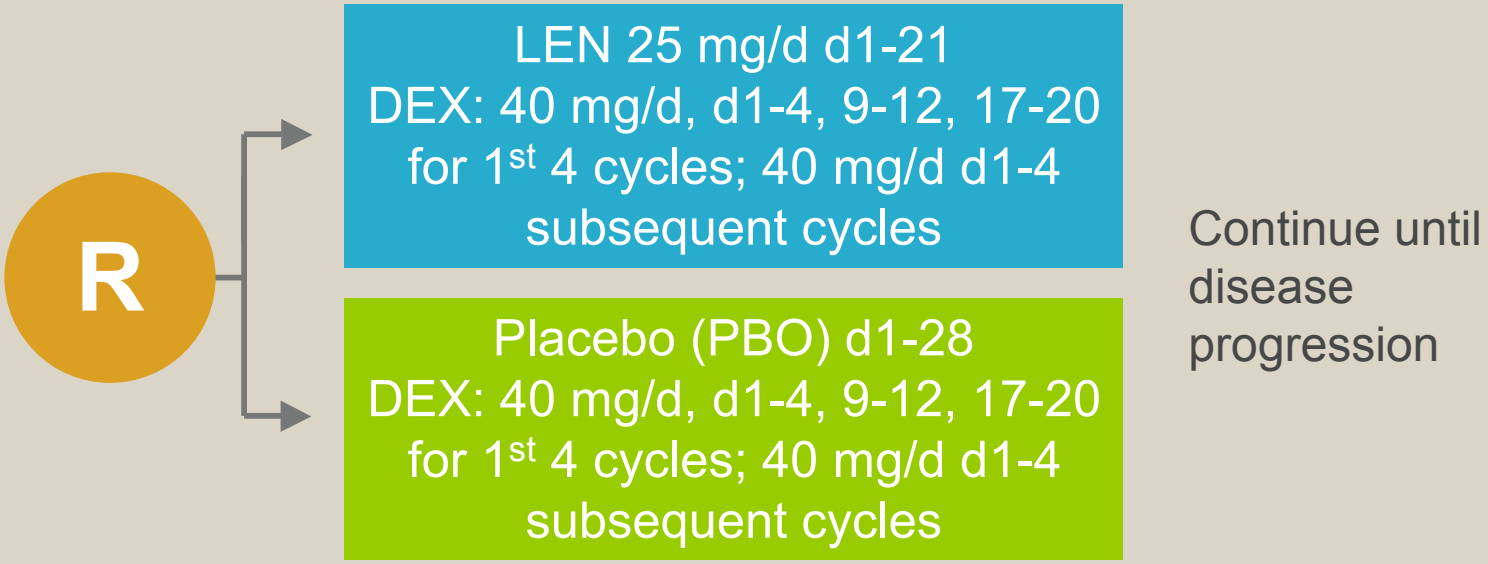
Lenalidomide and Dexamethasone (LEN plus DEX) Treatment in Relapsed/Refractory Multiple Myeloma Patients (Pts) and Risk of Secondary Primary Malignancies (SPM): Analysis of MM-009/010

Dimopoulos MA et al.

Proc ASCO 2011;Abstract 8009.

MM-009/010 Phase III Trial Schemas

Analysis of pooled data from patients with relapsed/refractory multiple myeloma (RRMM) treated in 2 Phase III studies (MM-009 and MM-010)



Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

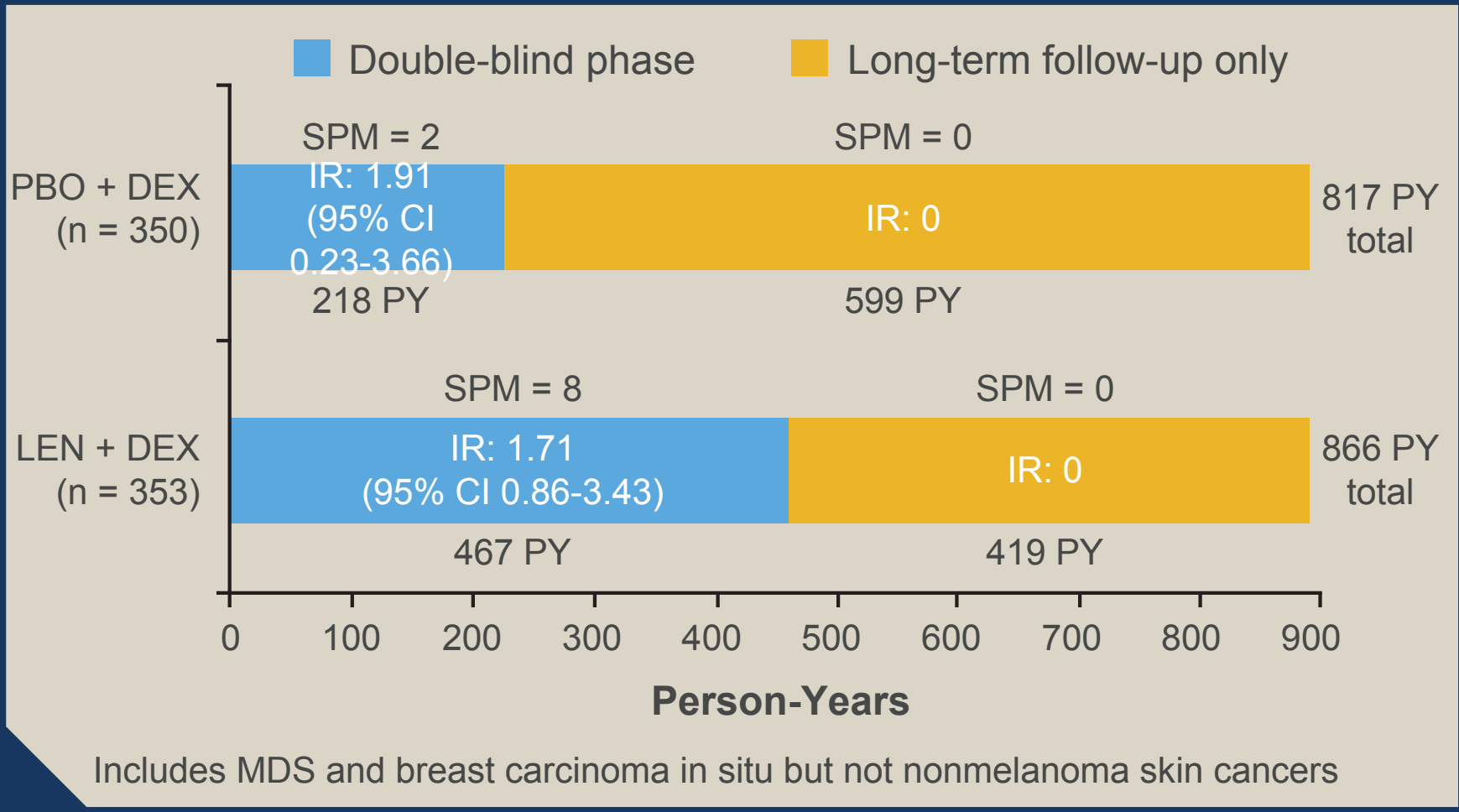
SPM Incidence Rates — Active Treatment Phase (Safety Population)

Invasive SPM	Incidence*	
	LEN + DEX (n = 353)	PBO + DEX (n = 350)
Hemtologic	0.42	0
AML/MDS	0.42	0
B-cell malignancies	0	0
Solid tumors	1.28	0.91
Noninvasive SPM		
Nonmelanoma skin cancer	2.40	0.91
Total SPM	3.98	1.38

* Incidence rate (IR) reported per 100 person-years (PY)

Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

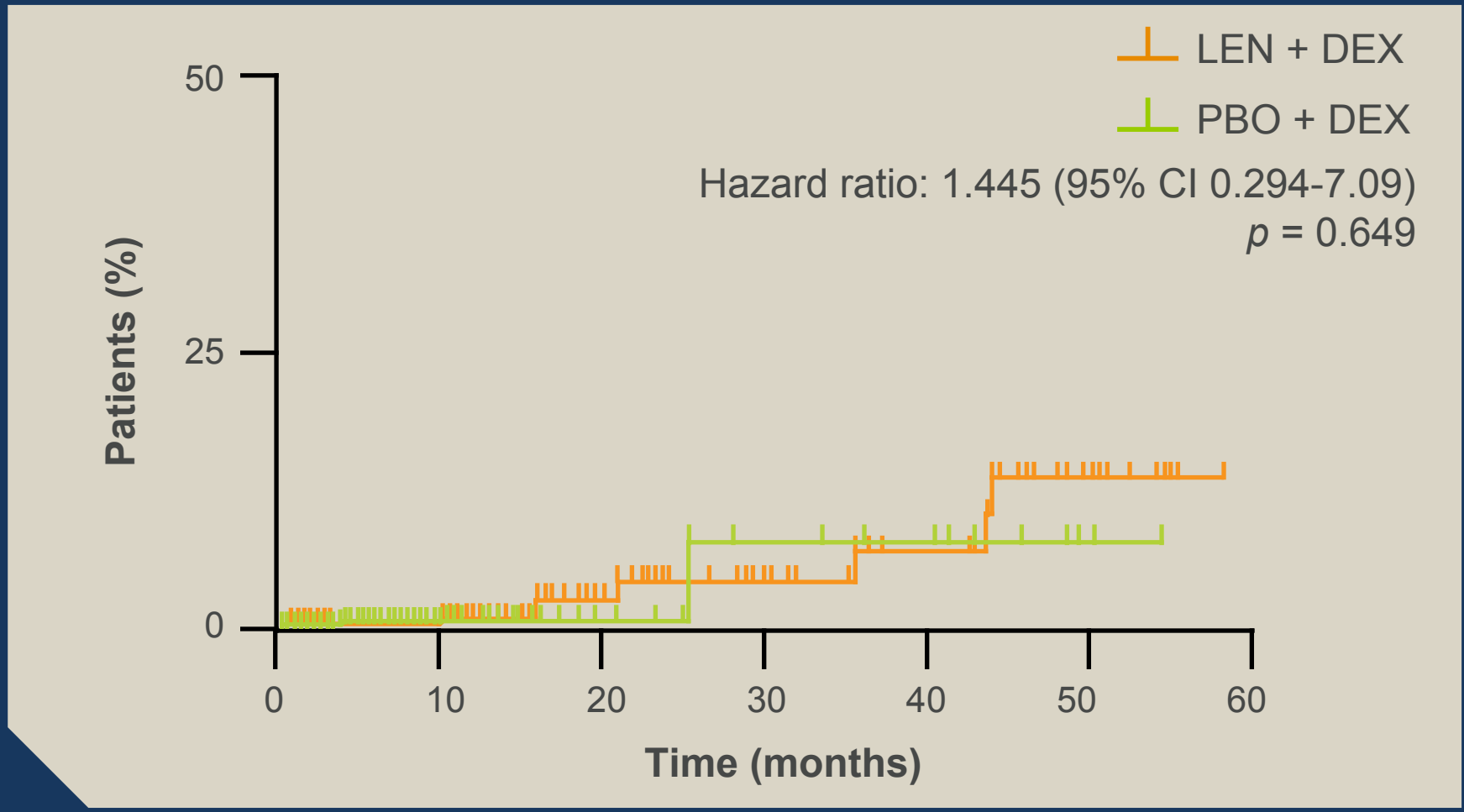
Invasive SPM Incidence Rates — Treatment and Follow-Up



Includes MDS and breast carcinoma in situ but not nonmelanoma skin cancers

With permission from Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

Time to Invasive SPM — Treatment Period



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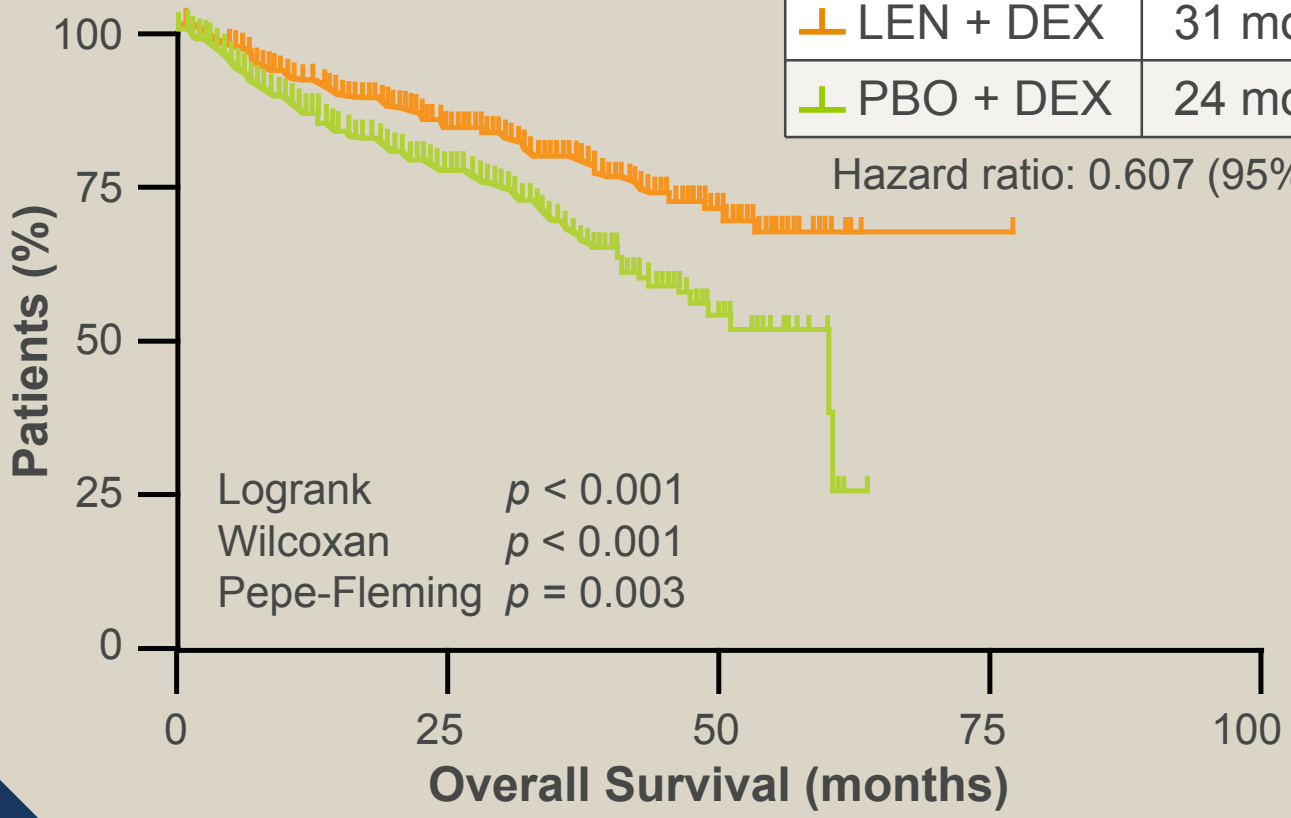
LEN + DEX Overall Survival (OS) (Up to Unblinding)

Treatment	Median OS	*p*-value
LEN + DEX	31 months	<0.001
PBO + DEX	24 months	

Hazard ratio: 0.607 (95% CI 0.459-0.803)



With permission from Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

Author Conclusions

- No difference in incidence rates of invasive SPMs in LEN + DEX arm versus PBO + DEX arm in MM-009/010
- SPM incidence rates were low and similar to the background incidence among persons similarly aged in the general population
- Overall survival was significantly longer for patients who received LEN + DEX
  - Confirmed with long-term follow-up despite ~50% of patients in the PBO + DEX arm crossing over to receive LEN-based therapy
- The overall benefit-risk profile of LEN in RRMM remains strongly positive

Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

Faculty Comments

DR BENSINGER: A signal of increased second primary cancer has been seen with lenalidomide in some of the maintenance trials. This retrospective pooled analysis found that no statistically significant difference was observed in the numbers of second primary tumors in patients with relapsed/refractory myeloma who received lenalidomide/dexamethasone versus those who received dexamethasone and placebo. This adds assurance to the idea that lenalidomide by itself may not increase the incidence of second primary cancer. An issue I would have liked to have seen addressed is whether prior melphalan exposure has any effect on the incidence of second primary cancer. In discussions of maintenance therapy, prior melphalan exposure is brought up as having a possible interaction.

Efficacy and Safety of Once-Weekly Bortezomib in Multiple Myeloma Patients

Bringhen S et al.
Blood 2010;116(23):4745-53.

Introduction

- The Phase III GIMEMA trial comparing VMPT-VT to VMP for elderly patients with newly diagnosed myeloma reported VMPT-VT was superior in response rate (complete response rate: 38% versus 24%) and progression-free survival (56% versus 41%) (*J Clin Oncol* 2010;28:5101-9).
- Although patients on both arms initially received twice-weekly bortezomib, the protocol was amended to evaluate whether once-weekly bortezomib could decrease toxicity while maintaining efficacy.
- Current analysis objective: To assess the effect of bortezomib schedule change on clinical outcomes and safety, specifically on the incidence and reversibility of bortezomib-induced peripheral neuropathy (PN), for patients enrolled in GIMEMA.

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Survival and Best Response Rates

	Once-weekly bortezomib (n = 369)	Twice-weekly bortezomib (n = 134)	*p*-value
3-year progression-free survival	50%	47%	1.0
3-year overall survival	88%	89%	0.54
Overall response rate	85%	86%	0.78
Complete response	30%	35%	0.27
Very good partial response	25%	19%	0.15
Partial response	30%	32%	0.66
Stable disease	13%	9%	0.27

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Bortezomib Treatment Exposure and Select Grade 3 or 4 Adverse Events (AEs)

	Once weekly (n = 369)	Twice weekly (n = 134)	*p*-value
Cumulative planned dose	46.8 mg/m^2	67.6 mg/m^2	—
Median cumulative dose delivered	39.4 mg/m^2	40.1 mg/m^2	0.65
Planned dose delivered	84%	59%	—
Patients who received ≥90% of planned dose	39%	13%	<0.001
Nonhematologic AE Neuropathy Sensory neuropathy	35% 8% 3%	51% 28% 16%	0.003 <0.001 <0.001
Dermatologic events	2%	7%	0.006

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Features of Peripheral Neuropathy

	Once weekly	Twice weekly	*p*-value
Cumulative proportion of patients with PN at 18 months			
Any grade Sensory neuropathy	40% 27%	72% 46%	<0.001 <0.001
Grade 3 or 4 Sensory neuropathy	9% 4%	36% 21%	<0.001 <0.001
Bortezomib dose modification caused by PN			
Dose reduction	17%	41%	<0.001
Dose discontinuation	5%	15%	<0.001
Median time to dose reduction	3.8 mo	2.8 mo	0.08

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Features of Peripheral Neuropathy (continued)

	Once weekly (n = 77)	Twice weekly (n = 73)	*p*-value
Outcome of Grade 2-4 PN			
Resolution	34%	40%	**0.74**
Improvement	30%	26%	—
Persistence	36%	34%	—
Median time to recovery	2.3 mo	3.2 mo	0.005

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Author Conclusions

- Once-weekly infusion of bortezomib in combination with MPT is a valuable treatment schedule for elderly patients with newly diagnosed disease.
- Initial twice-weekly bortezomib followed by a rapid reduction to a once-weekly schedule may be suggested in selected patients with clinically aggressive disease (ie, those with incipient renal failure or extensive pain) (data not shown).
- The once-weekly schedule significantly reduced the incidence of PN and decreased the rate of discontinuation compared to the twice-weekly schedule, resulting in similar cumulative bortezomib doses in the 2 groups.
- The improvement in the safety profile was not associated with any reduction in the efficacy of the regimen.

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Faculty Comments

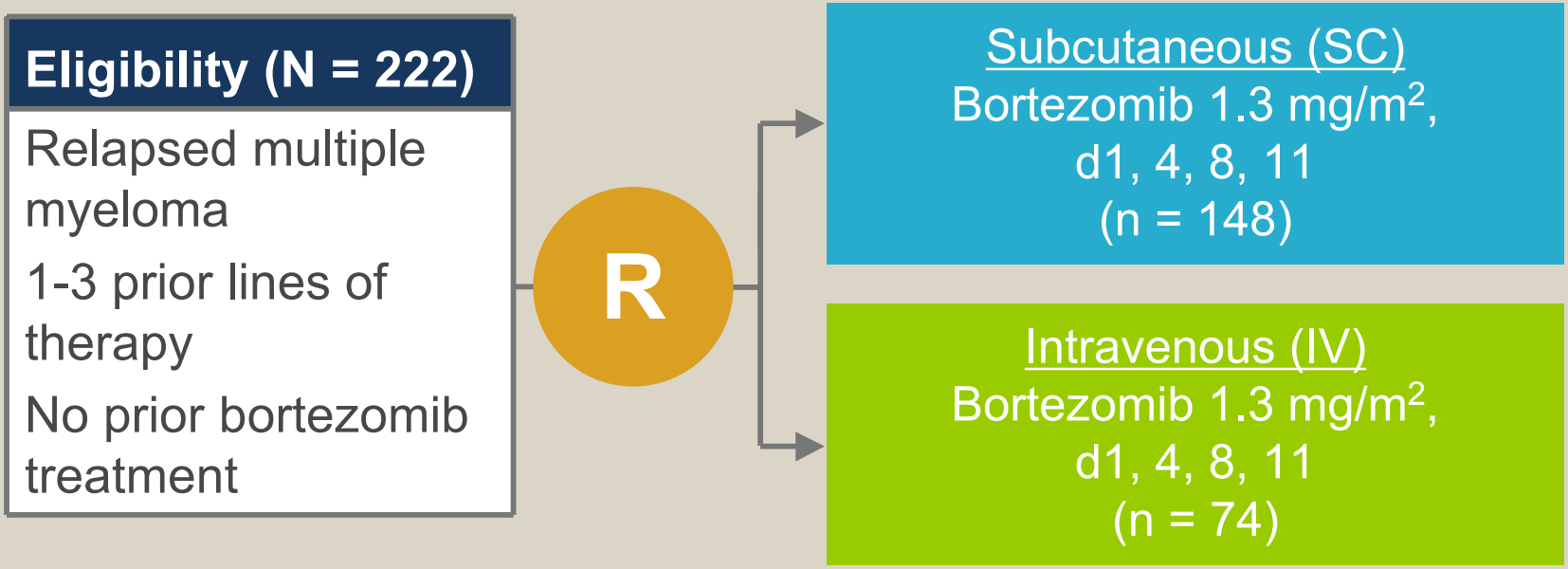
DR ZONDER: This analysis of the VMP versus VMPT-VT study published in *Blood* focuses on the incidences of peripheral neuropathy (PN) with weekly versus twice-weekly bortezomib administration on the trial. A large reduction was evident in the incidence of Grade 3 and 4 PN in addition to discontinuations related to PN.

Similar data exist from the Mayo Clinic on the use of once- versus twice-weekly bortezomib with similar results — less neuropathy, same efficacy. When I administer bortezomib with MP or with cyclophosphamide/dexamethasone, I use the once-weekly schedule.

Subcutaneous versus Intravenous Administration of Bortezomib in Patients with Relapsed Multiple Myeloma: A Randomised, Phase 3, Non-Inferiority Study

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

Phase III Trial of Subcutaneous versus Intravenous Bortezomib Administration



Up to 8 treatment cycles (plus 2 cycles if SD or PR)

If <CR after 4 cycles, 20 mg dexamethasone on days 1, 2, 4, 5, 8, 9, 11, 12 added in the next 4 cycles

SD = stable disease; PR = partial response; CR = complete response

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

Treatment Exposure

	Bortezomib SC (n = 147)*	Bortezomib IV (n = 74)
Median number of cycles (range)	8 (1-10)	8 (1-10)
Median time on study	22.6 weeks	22.6 weeks
Median cumulative bortezomib dose	33.76 mg/m^2	31.46 mg/m^2
Patients receiving dexamethasone	82 (56%)	39 (53%)

* Three patients had protocol violations for route of administration.

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

Primary Endpoint: Overall Response Rate After 4 Cycles

Clinical variable	Bortezomib SC (n = 145)*	Bortezomib IV (n = 73)*
Overall response rate†	42%	42%
Complete response	6%	8%
Partial response	36%	34%
Very good partial response	4%	3%

* Three patients in the SC group and 1 patient in the IV group were not evaluable for response.
† *p*-value of 0.002 meets prespecified criteria for fulfilling noninferiority hypothesis of SC versus IV bortezomib.

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

Additional Efficacy Outcomes

Responding patients (after 8 cycles)	Bortezomib SC (n = 76)	Bortezomib IV (n = 38)
Median time to first response	1.4 mo	1.4 mo
Median time to best response	1.6 mo	1.5 mo
Median duration of response	9.7 mo	8.7 mo
Intent-to-treat population	**(n = 148)**	**(n = 74)**
Median time to progression	10.4 mo	9.4 mo
Median progression-free survival	10.2 mo	8.0 mo
1-year overall survival rate	72.6%	76.7%

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

Select Grade ≥3 Adverse Events

Adverse event	Bortezomib SC (n = 147)	Bortezomib IV (n = 74)
Any treatment-related adverse event	39%	55%
Neutropenia	18%	18%
Thrombocytopenia	13%	19%
Anemia	12%	8%
Leukopenia	6%	7%
Peripheral sensory neuropathy	**5%**	**15%**

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

Author Conclusions

- SC bortezomib was noninferior in terms of efficacy compared to IV administration.
- The pharmacokinetic and pharmacodynamic profiles of SC and IV bortezomib are similar (data not shown).
- SC administration of bortezomib appears to have an improved safety profile compared to IV administration.
  - Significantly lower rates of peripheral neuropathy of all grades were observed in patients administered SC bortezomib.

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

Faculty Comments

DR BENSINGER: This is a nice IFM trial in which patients with relapsed, bortezomib-naïve disease were randomly assigned to receive either subcutaneous (SC) or intravenous (IV) bortezomib. No major differences in the pharmacokinetics of SC versus IV administration were observed. Patient outcomes were also similar — response rates, time to progression and overall survival were identical.

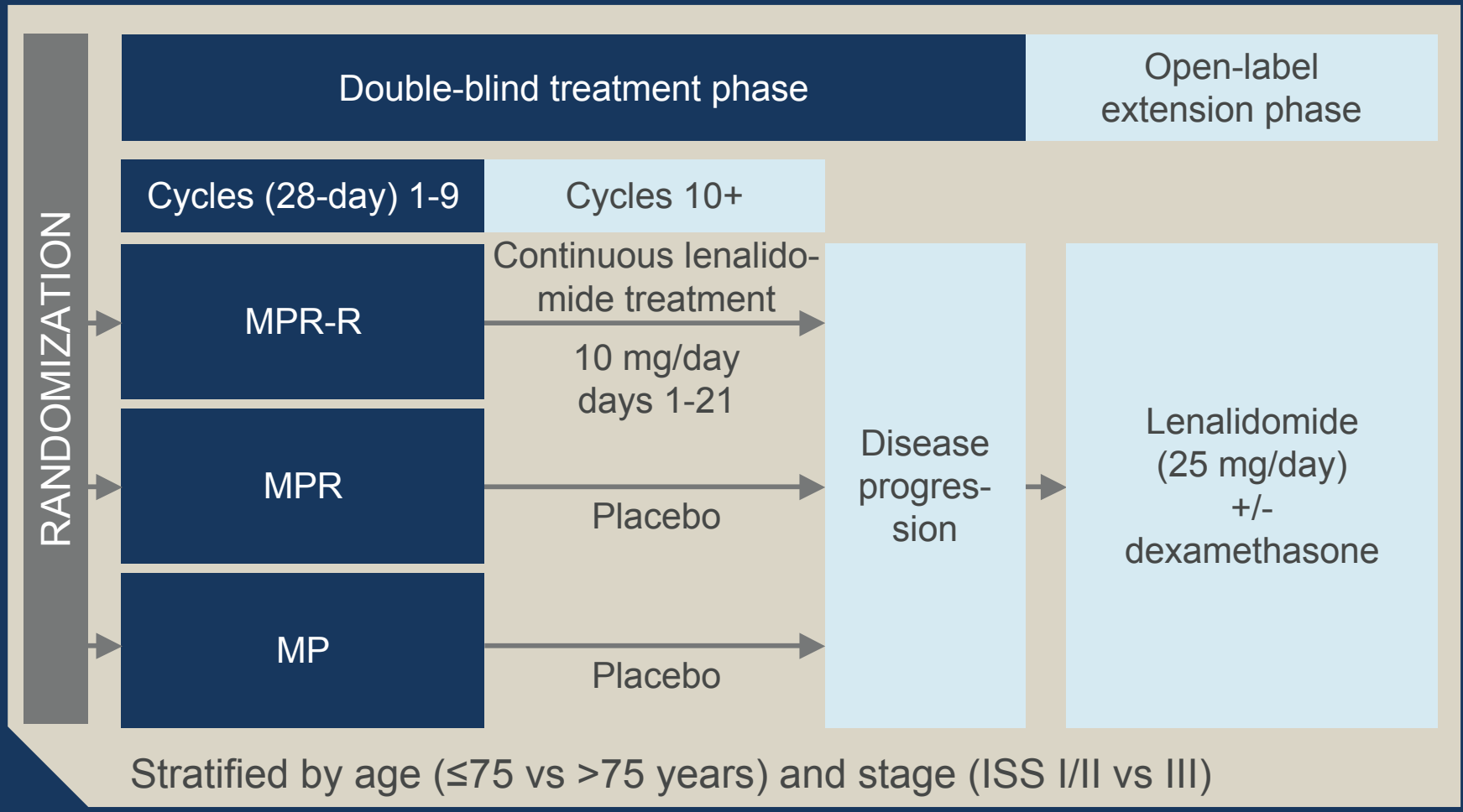
The interesting finding of this study is that SC bortezomib caused less toxicity, specifically less neurotoxicity. A trend toward fewer cytopenias was also observed. The take-home message for me is that SC bortezomib is equally efficacious to IV, and it is associated with less neurotoxicity and is potentially more convenient. I have adopted SC bortezomib in my practice.

A Phase III 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.

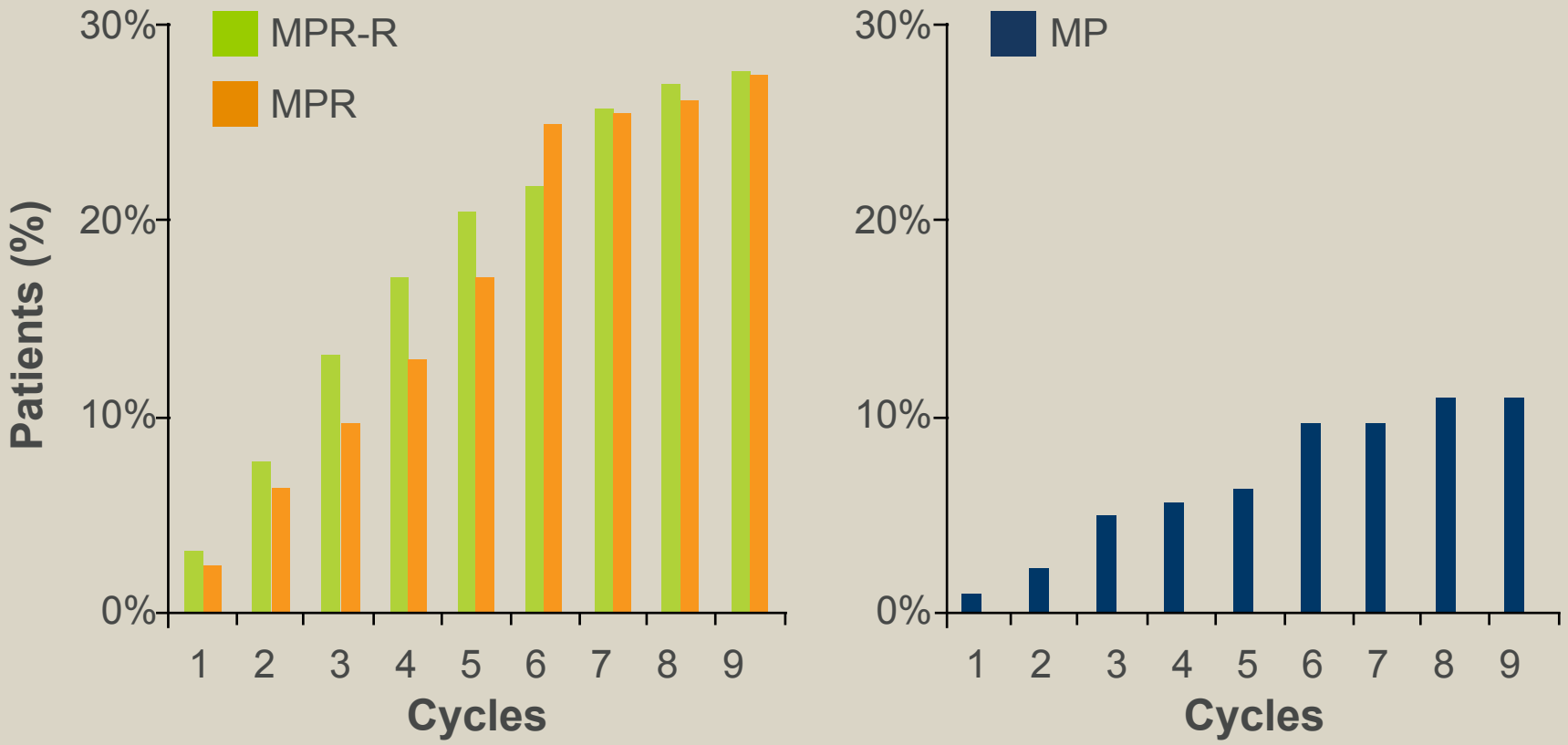
Proc ASH 2010;Abstract 622.

Study Design



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

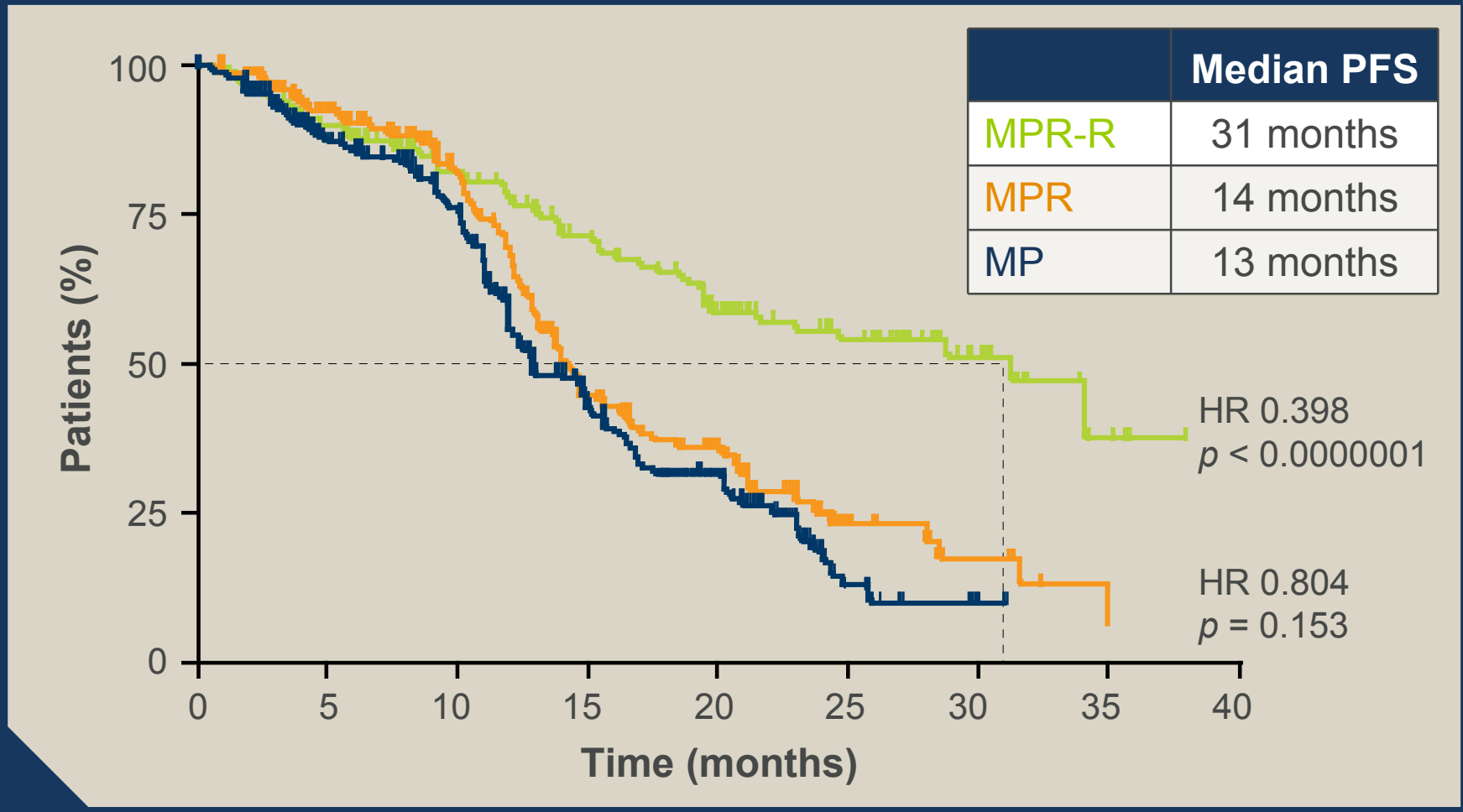
Response Rate



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 (25 Months Follow-Up)



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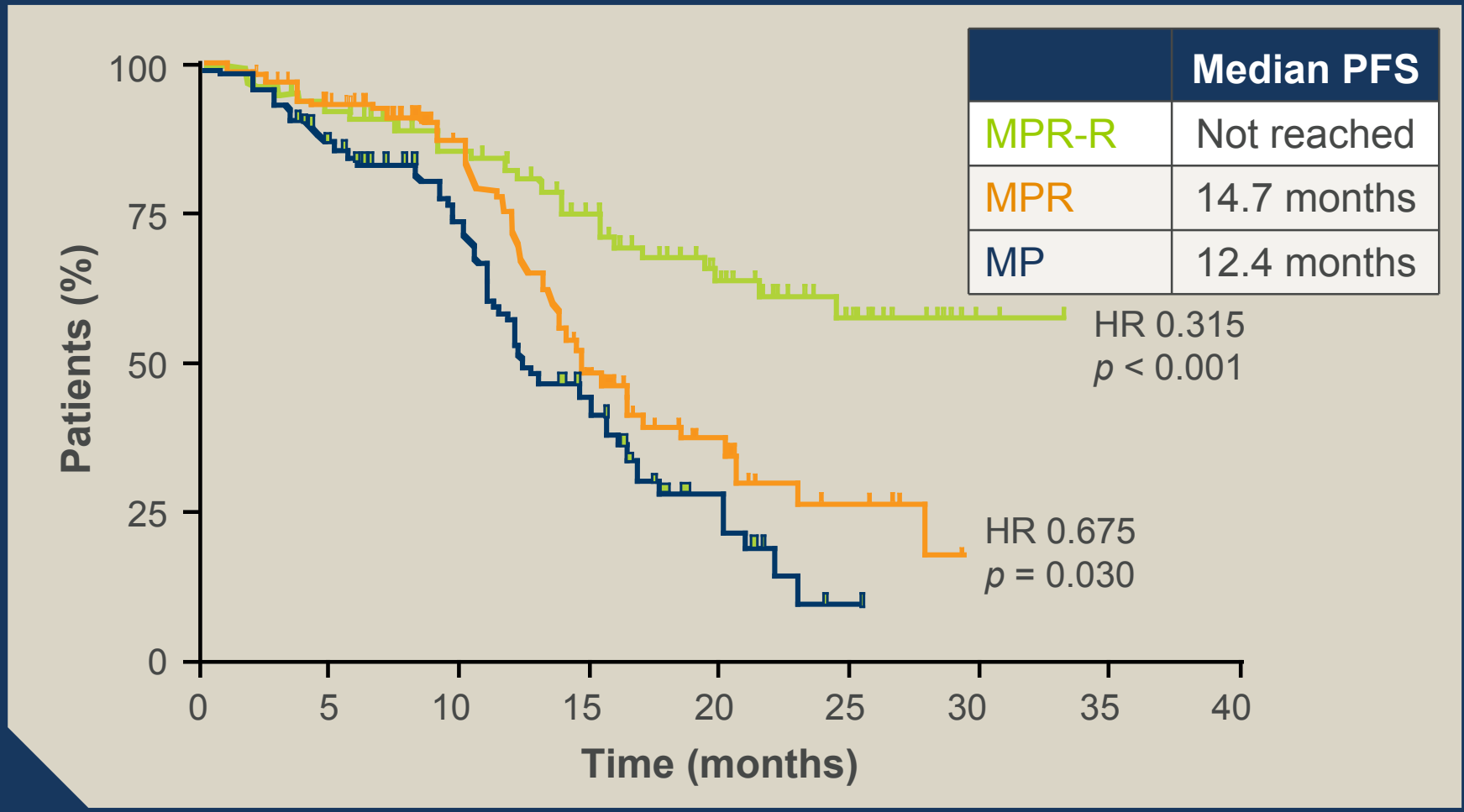
Progression-Free Survival (PFS)
Patients Age 65-75 Years



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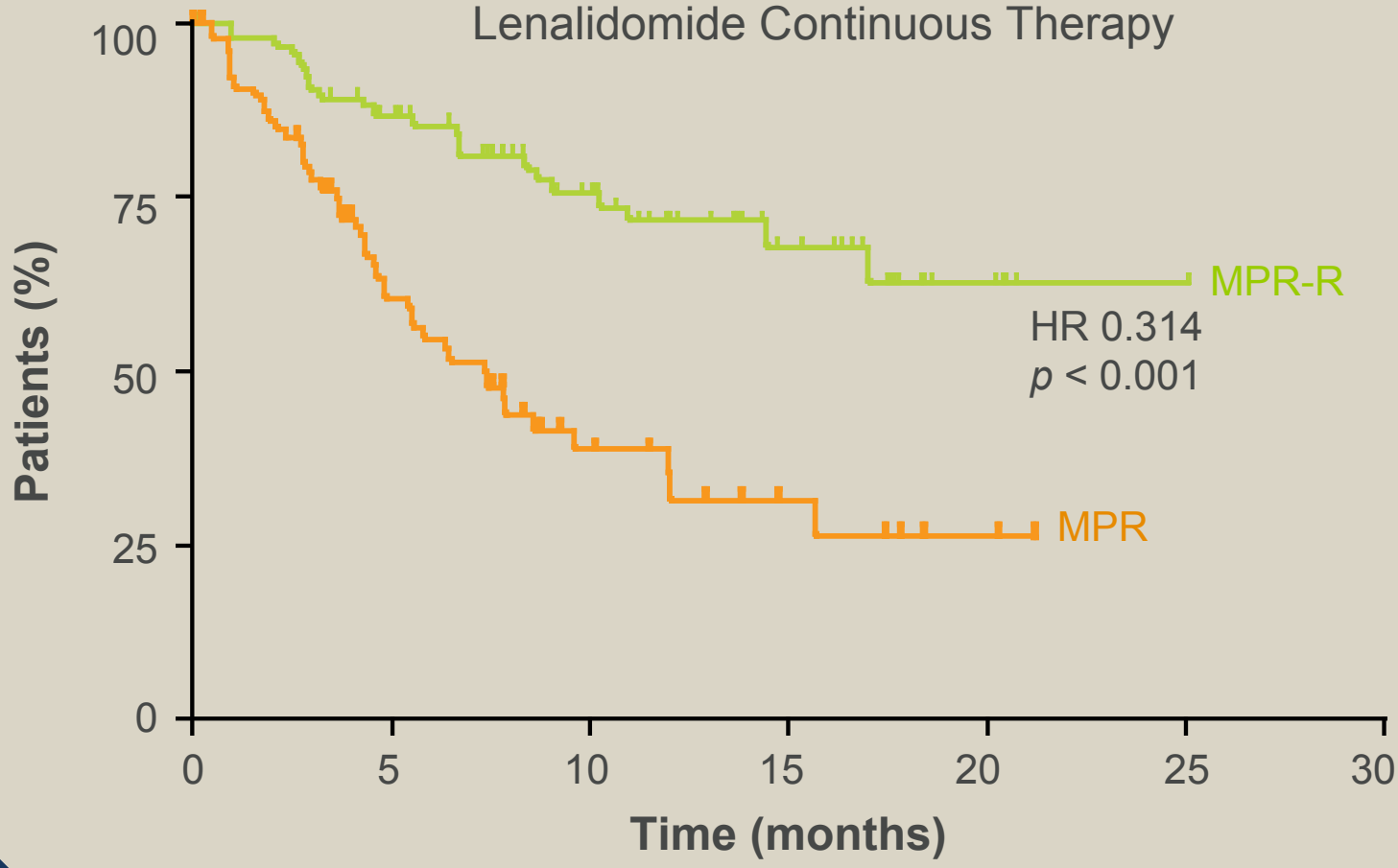
Landmark Analysis — PFS



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

Author Conclusions

- Patients receiving MPR-R for NDMM achieved a higher overall response rate, as well as better-quality and more rapid responses versus MP.
- MPR-R compared to 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.

Faculty Comments

DR ZONDER: This study compared MP to MP with lenalidomide (R) and MPR followed by R. These data indicate how important it is to continue lenalidomide therapy. One disappointing aspect about this study was that even though the overall response rates were similar between the 2 MPR arms, that did not translate into a clinically significant improvement in duration of response compared to MP alone. That surprises me.

If it turns out that an exponential increase of secondary cancer occurs beyond 2 or 3 years, then we'll certainly have to figure out what the optimal duration of therapy is, but right now it would seem that the optimal duration of lenalidomide therapy is until disease progression.

Bortezomib-Based Induction Therapy Followed by Autologous Stem Cell Transplantation and Maintenance Therapy with Bortezomib Improves Outcome in Myeloma Patients with Gain 1q21 and t(4;14) — A Subgroup Analysis of the HOVON-65/GMMG-HD4 Trial

Goldschmidt H et al.

Proc ASH 2010;Abstract 305.

HOVON-65/GMMG-HD4 Trial: Background and Methods

- Chromosomal aberrations are important prognostic parameters in multiple myeloma.
- This analysis evaluated the association of FISH results and outcome of a subgroup of patients within the HOVON-65/ GMMG-HD4 trial.
- **Arm A (n = 131):** Vincristine/doxorubicin/dexamethasone (VAD) x 3 with autologous stem cell transplant (ASCT) ➔ thalidomide ≤2 years
- **Arm B (n = 127):** Bortezomib/doxorubicin/dexamethasone (PAD) x 3 with ASCT ➔ bortezomib ≤2 years
- All patients received: Hematopoietic stem cell mobilization with CAD and G-CSF and 1-2 cycles of high-dose melphalan with ASCT ➔ maintenance therapy

Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

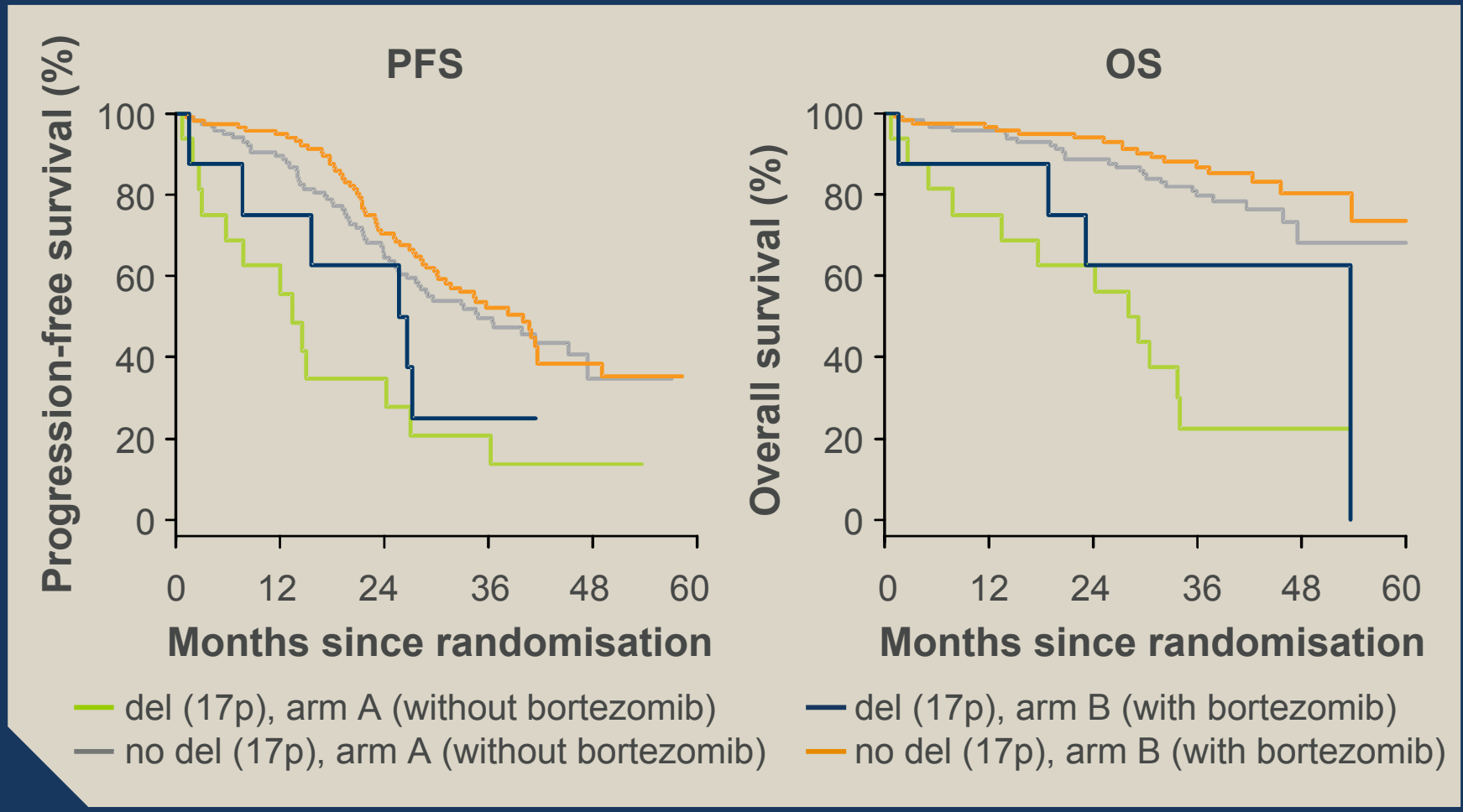
Prognostic Effect of Chromosomal Abnormalities on Outcome

	PFS at 36 months			OS at 36 months		
	Present	Absent	*p*-value	Present	Absent	*p*-value
del(8p21)	34%	54%	0.005	67%	83%	NS
del(13q14)	39%	58%	0.010	73%	84%	0.006
del(17p13)	22%	51%	<0.001	36%	83%	<0.001
+1q21	22%	56%	0.002	71%	84%	0.010
t(4;14)	31%	51%	0.020	55%	83%	<0.001

PFS = progression-free survival; OS = overall survival;
NS = not significant

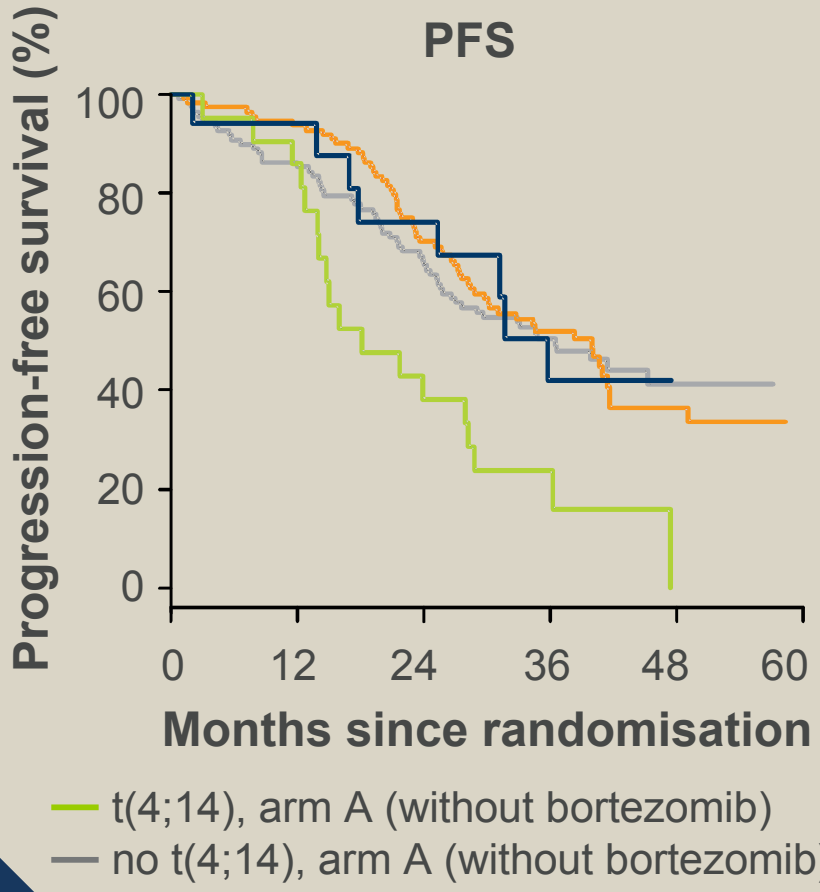
Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

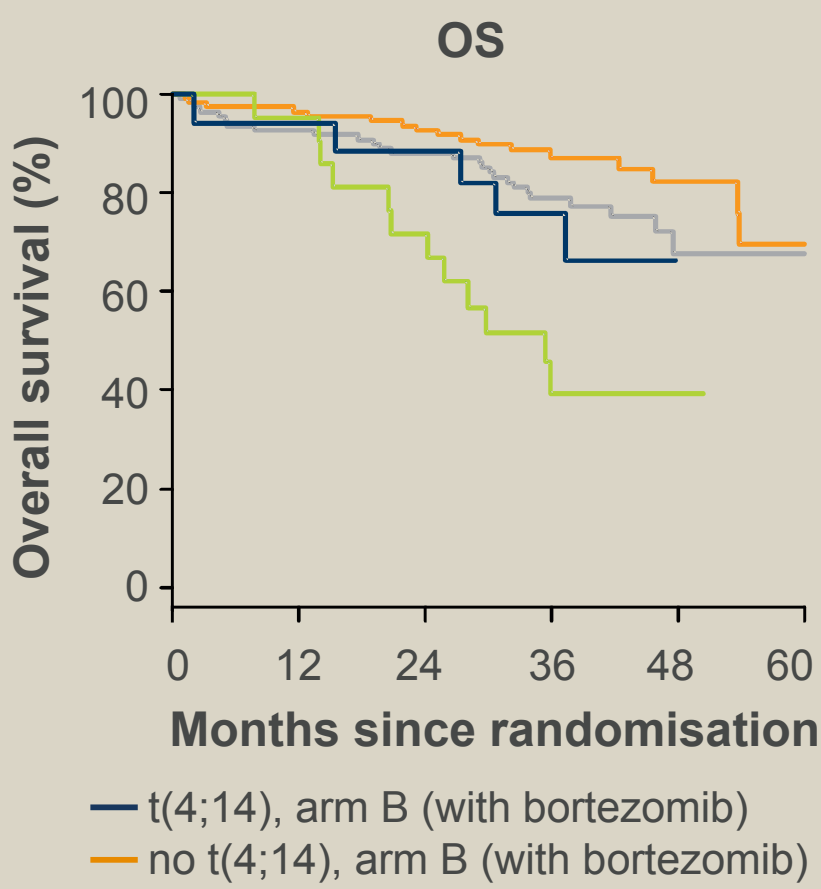
Comparison between Both Study Arms Deletion 17p13



With permission from Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

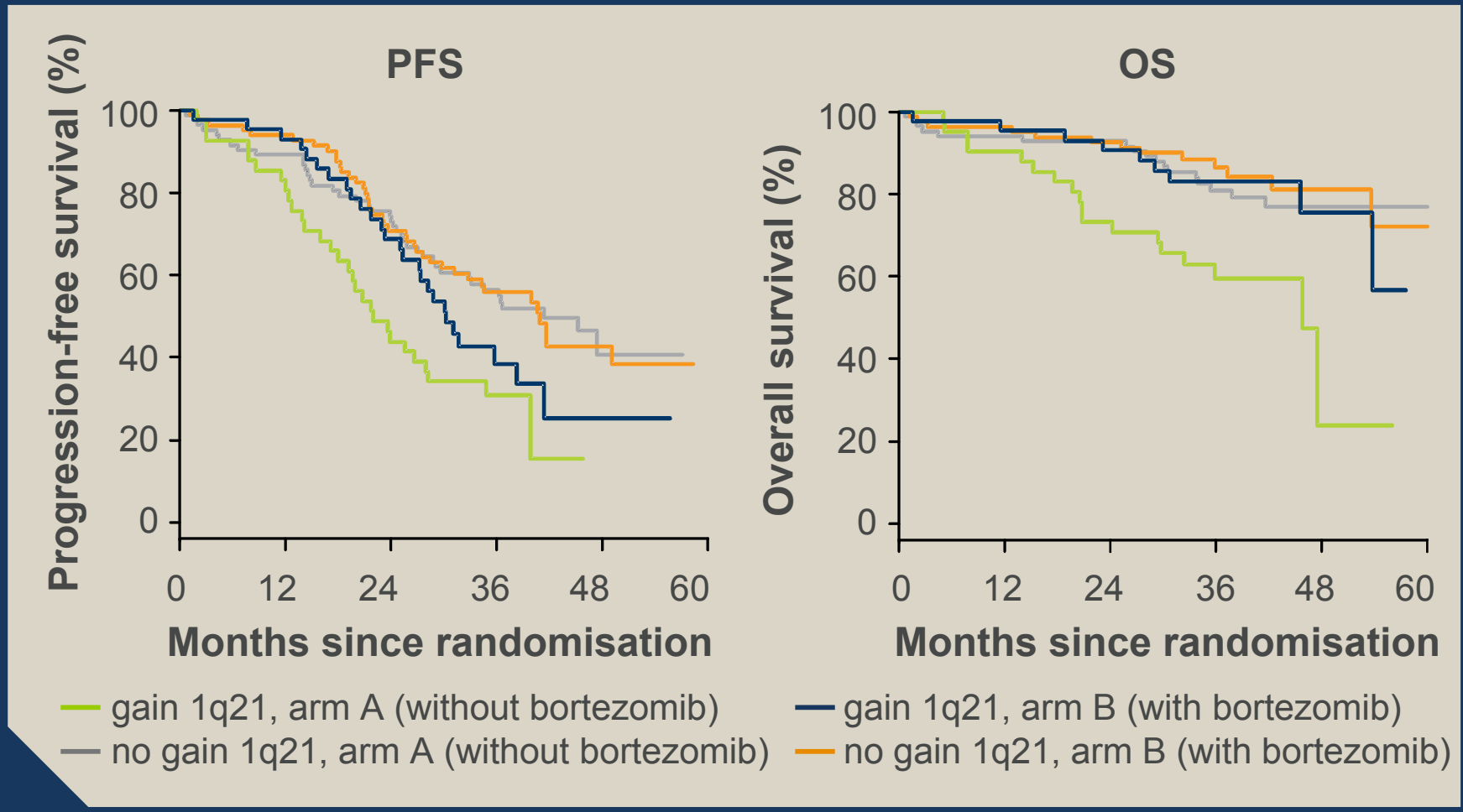
Comparison between Both Study Arms Translocation t(4;14)





With permission from Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

Comparison between Both Study Arms Gain 1q21



With permission from Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

Author Conclusions

- Chromosomal aberrations with prognostic effect on PFS and OS within the GMMG-HD4 trial were as follows:
  - del(13q), del(17p), t(4;14) and +1q
- Deletion of chromosome 13q as exclusive chromosomal aberration without the presence of del(17p) and t(4;14) indicates no effect on outcome.
- These data indicate that ASCT and maintenance therapy with bortezomib significantly improve outcome in patients with myeloma with gain 1q and t(4;14).
- In contrast, ASCT and maintenance therapy with bortezomib do not modify the outcome of patients with del(17p), for whom a standard therapy has yet to be identified.

Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

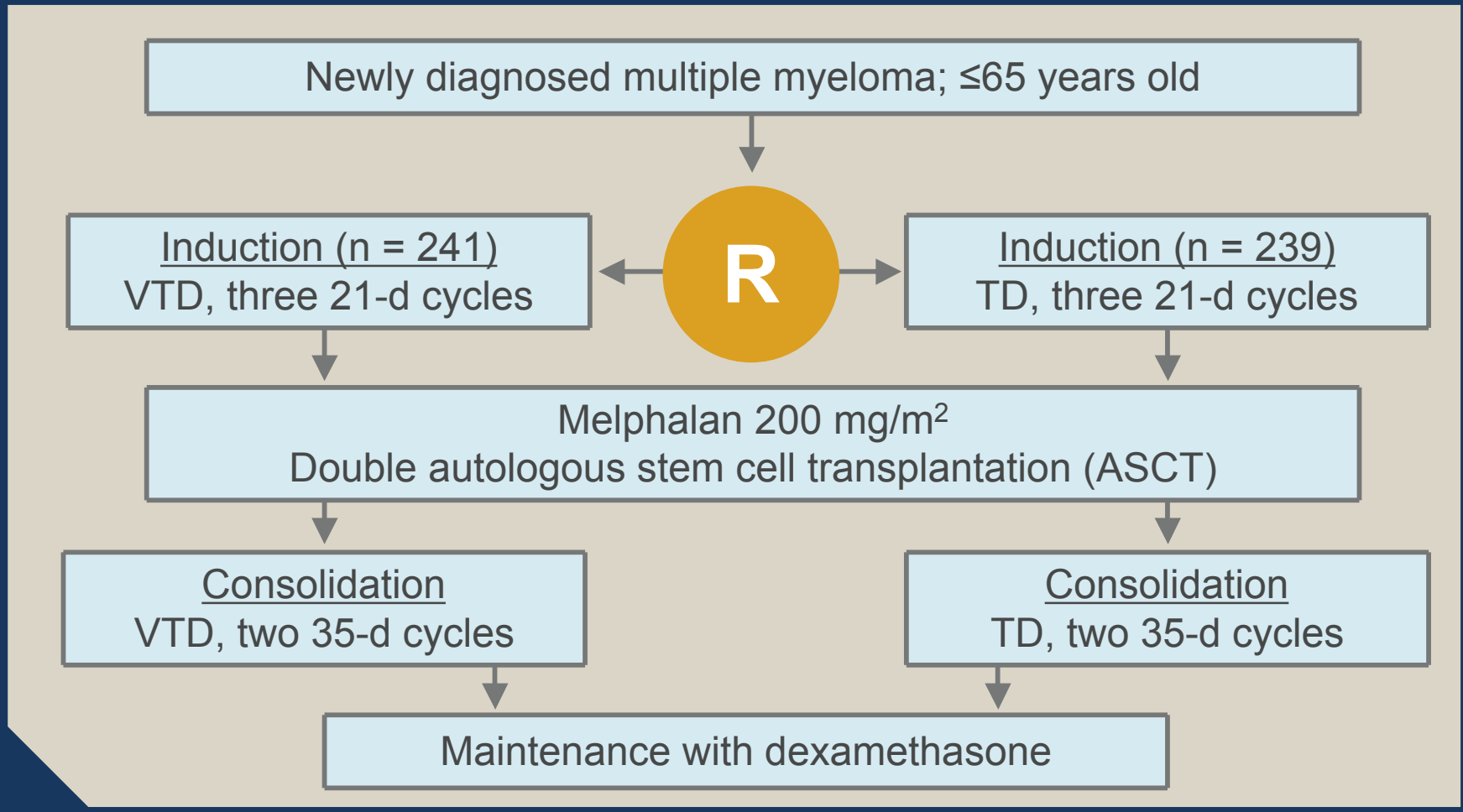
Faculty Comments

DR WOLF: This report focuses on a subgroup analysis of the HOVON study and on the ability of bortezomib to overcome adverse prognostic features. Patients with t(4;14) who received VAD have poor prognoses, with a median progression-free survival time half as long as those without the translocation, yet no such negative effect was observed in patients on the PAD arm. PAD also resulted in improved 3-year overall survival for patients with t(4;14). If you compare VAD to PAD, an advantage was evident, but it was much smaller in those without the 4;14 translocation. The message here confirms that bortezomib overcomes the adverse prognostic features of the 4;14 translocation. A new observation is that patients with overexpression of the 1q21 gene have a poor prognosis.

Bortezomib with Thalidomide plus Dexamethasone Compared with Thalidomide plus Dexamethasone as Induction Therapy Before, and Consolidation Therapy After, Double Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Randomized Phase 3 Study

Cavo M et al.
Lancet 2010;376(9758):2075-85.

Trial Schema



Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Response to Induction Therapy Intent-to-Treat Analysis

	VTD (n = 236)	TD (n = 238)	*p*-value
Complete response (CR)	19%	5%	<0.0001
CR + near CR (nCR)	31%	11%	<0.0001
≥Very good partial response	62%	28%	<0.0001
≥Partial response	93%	79%	0.0011
Minimal response or stable disease	7%	16%	0.0011
Progressive disease	0%	5%	0.005

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Response After Second ASCT

	VTD (n = 236)	TD (n = 238)	*p*-value
CR	42%	30%	0.0105
CR + nCR	55%	41%	0.0024
≥Very good partial response	82%	64%	<0.0001
≥Partial response	93%	84%	<0.0011
Minimal response or stable disease	6%	8%	0.38
Progressive disease	1%	8%	0.0001

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Progression-Free Survival (PFS) in Patients with Poor Prognoses

	VTD	TD	*p*-value
Estimated 3-year PFS	68%	56%	0.0057
Events/number of patients			
Presense of del(13q)	29/103	46/103	0.0039
LDH >190 U/L	43/182	72/200	0.0088
Age >60 years	23/92	41/95	0.0150
Presence of t(4;14) ± del(17q)	20/53	32/57	0.0174
Bone marrow plasma cells >50%	30/116	41/111	0.0301
ISS disease Stage II-III	42/129	57/131	0.0482

LDH = lactate dehydrogenase

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Select Grade 3 or 4 Adverse Events (AEs) During Induction Therapy

	VTD (n = 236)	TD (n = 238)	*p*-value
Any serious AE	13%	13%	0.86
Any Grade 3 or 4 AE	56%	33%	<0.0001
Any Grade 3 or 4 non-hematologic AE	51%	31%	<0.0001
Peripheral neuropathy (PN)*	10%	2%	0.0004
Skin rash	10%	2%	0.0001
Gastrointestinal events	2%	<1%	0.0982

* Resolution or improvement of severe PN was recorded in 18 of 23 patients receiving VTD and in 3 of 5 patients receiving TD.

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Author Conclusions

- In this patient population induction and consolidation therapy with VTD significantly improved clinical outcomes compared to TD therapy in those receiving double ASCT.
  - CR/nCR rate: 31% (VTD) versus 11% (TD); *p*-value < 0.0001
- VTD combined with double ASCT had a positive effect on PFS in patients with poor prognoses, including those with adverse cytogenetic abnormalities who do not benefit from standard ASCT.
- VTD represents a new standard to maximize the degree and speed of tumor reduction in patients with myeloma who are eligible for transplant.

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Faculty Comments

DR ZONDER: This up-front study randomly assigned patients with multiple myeloma eligible for transplant to VTD or TD. The study demonstrated that VTD was superior overall to TD. The percent of patients who had a complete response (CR) or near CR (nCR) after induction was 3 times higher on the VTD arm, and the rate of partial response or better was 93% versus 79%.

That benefit seems to carry through transplant. Outside the setting of a study, it appears that VTD is superior to TD, but even with that combination, you can improve responses in patients who aren't in a CR or nCR by sending them for transplant.

Stem Cell Mobilization in Patients with Newly Diagnosed Multiple Myeloma After Lenalidomide Induction Therapy

Cavallo F et al.
Leukemia 2011;25(10):1627-31.

Background

- The mobilization of stem cells may be adversely affected by cytopenias associated with the use of lenalidomide in patients with multiple myeloma (MM).
- Median yield of stem cells collected after lenalidomide/ dexamethasone (Rd) induction is lower in patients mobilized with granulocyte-colony stimulating factor (G-CSF) alone compared to patients mobilized with cyclophosphamide and G-CSF (*Leukemia* 2007;21:2035).
- The hematologic toxicity observed during treatment with lenalidomide has raised concern that its use may negatively affect the ability to mobilize stem cells (*Leukemia* 2007;21:2035).

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Methods and Objective

- Rd induction therapy was administered in a multicenter, prospective study (RV-MM-PI209) for patients with newly diagnosed MM.
- Patients were then mobilized and randomly assigned to receive oral MPR (melphalan/prednisone/lenalidomide) or high-dose melphalan and tandem autologous stem cell transplant (ASCT).
- The objective of this study was to investigate the influence of 4 cycles of Rd induction therapy on stem cell collection.

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Stem Cell Harvest — All Evaluable Patients

	n = 331
Median duration of leukapheresis	3 days
Median cells collected after 1 mobilization cycle (x 10^6 $CD34^+$/kg)	7.8
Median cells collected after 2 mobilization cycles (x 10^6 $CD34^+$/kg)	8.7
Patients with yields <2 x 10^6 $CD34^+$/kg at 1st mobilization*	15%
Patients with yields <4 x 10^6 $CD34^+$/kg at 1st mobilization	21%
Patients with yields <2 x 10^6 $CD34^+$/kg at 2nd mobilization	8%
Patients with yields <4 x 10^6 $CD34^+$/kg at 2nd mobilization	9%

* Inadequate yield defined as <4x10^6 $CD34^+$/kg

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Engraftment at First ASCT

	n = 143*
Median x 10^6 $CD34^+$/kg cells infused	4.30
Days until absolute neutrophil count >500 x 10^9/L Median	8
Days until platelet count >25 x 10^9/L Median	7.5
Red blood cell transfusion	36%
Platelet transfusion	59%

* Patients in the evaluable population who received Rd induction therapy

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Stem Cell Mobilization Summary

Inadequate yield after first mobilization	21%
Inadequate yield after second mobilization	9%
Patients able to obtain sufficient stem cell harvests (at the end of the mobilization phase)	91%

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Author Conclusions

- Lenalidomide as part of an induction regimen did not adversely affect stem cell mobilization.
- The quantity of stem cells collected was adequate to perform tandem ASCT in 91% of patients with rapid and successful engraftment in all patients.
- This is the largest prospective study reporting on stem cell collection after Rd induction before ASCT in patients with newly diagnosed MM.

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Faculty Comments

DR ZONDER: Concerns have arisen in the literature about the impact of lenalidomide on stem cell collection. This study evaluated 346 patients with newly diagnosed multiple myeloma who received 4 cycles of lenalidomide/dexamethasone (Rd) followed by stem cell collection with cyclophosphamide and G-CSF.

The authors reported that 79% of patients achieved sufficient yield with first mobilization. Upon second mobilization, 91% of patients achieved adequate yield.

The bottom line is we now have data that indicate that lenalidomide exposure does not have an effect on ability to mobilize stem cells and that the majority of patients are able to be adequately mobilized with 1 or 2 collection attempts.

Bortezomib, Melphalan, and Prednisone versus Bortezomib, Thalidomide, and Prednisone as Induction Therapy Followed by Maintenance Treatment with Bortezomib and Thalidomide versus Bortezomib and Prednisone in Elderly Patients with Untreated Multiple Myeloma: A Randomized Trial

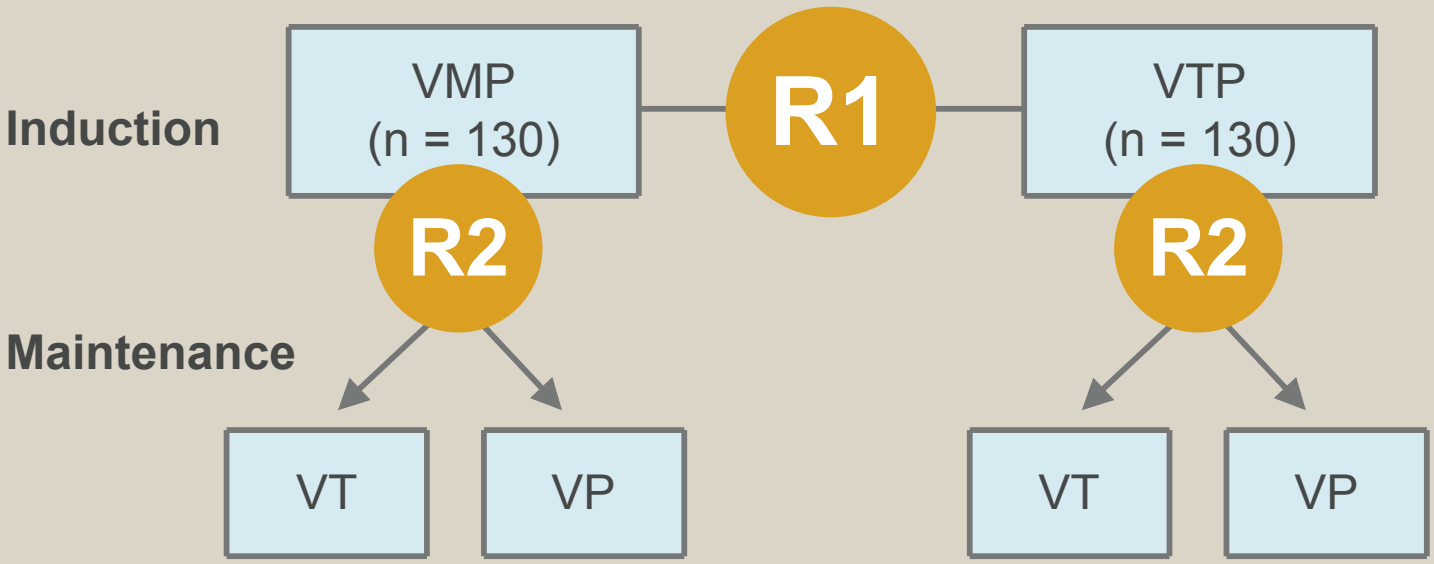
Mateos MV et al.
Lancet Oncol 2010;11(10):934-41.

Introduction

- Bortezomib, melphalan and prednisone (VMP) is tolerable and effective in elderly patients with multiple myeloma (MM).
  - 89% ≥overall response rate (ORR); 32% complete response (CR) (*Blood* 2006;108:2165)
  - Median progression-free survival = 27.2 months (*Haematologica* 2008;93:560)
  - 17% Grade 3 or 4 peripheral neuropathy
- Current study objectives
  - Induction: To achieve a CR rate of ≥20% and to determine whether melphalan or thalidomide was better in combination with bortezomib
  - Maintenance: To increase CR rate by ≥15% (from 20% after induction to 35%) with a favorable toxicity profile

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

VMP vs VTP Followed by VT vs VP for Untreated MM in Patients >65 Years



Bortezomib (V): Induction phase, 1.3 mg/m^2 twice weekly during a 6-week first cycle, then weekly during subsequent cycles; maintenance phase, 1.3 mg/m^2 twice weekly days 1, 4, 8 and 11 every 3 months

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Response Rate During Induction and Maintenance Therapy

Induction therapy	VMP (n = 130)	VTP (n = 130)	*p*-value
ORR (≥PR)	80%	81%	0.9
CR	20%	28%	0.2
Near CR	12%	8%	0.2
PR	48%	45%	0.7
Maintenance therapy	**VP (n = 87)**	**VT (n = 91)**	***p*-value**
CR	39%	44%	NS

NS = not significant

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Response in Hyperdiploid (HD) versus Nonhyperdiploid (NHD) Patients

Response	NHD (n = 92)	HD* (n = 132)	*p*-value
ORR	77%	83%	0.4
VMP group	82%	81%	0.7
VTP group	73%	86%	0.4
3-year overall survival (95% CI)	63%	77%	0.04
VMP group	72%	76%	0.5
VTP group	53%	77%	0.02

* HD patient group: DNA index >1.0 with assessments performed by flow cytometry

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Select Adverse Events (AEs) (Grade 3 or Worse)

Induction therapy	VMP (n = 130)	VTP (n = 130)	*p*-value
Thrombocytopenia	27%	12%	0.0001
Neutropenia	39%	22%	0.008
Peripheral neuropathy	7%	9%	0.6
Related serious AEs	15%	31%	0.01
Maintenance therapy	**VP (n = 87)**	**VT (n = 91)**	***p*-value**
Thrombocytopenia (Grade 1 or 2)	1%	1%	0.8
Gastrointestinal toxicity	1%	4%	0.6
Peripheral neuropathy	2%	7%	0.6
Discontinuation due to AEs	5%	8%	0.6

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Author Conclusions

- Reduced-intensity induction with a bortezomib-based regimen, followed by maintenance, is a safe and effective treatment for elderly patients with MM.
  - ORR, 80% (VMP) versus 81% (VTP); *p*-value = 0.9
- The rates of Grade 3 or worse peripheral neuropathy and gastrointestinal symptoms were similar compared to a conventional schedule of VMP.
- Maintenance therapy increased CR rates (VP: 39% versus VT: 44%).
- In contrast to VMP, VTP induction was associated with a higher occurrence of serious AEs.

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Faculty Comments

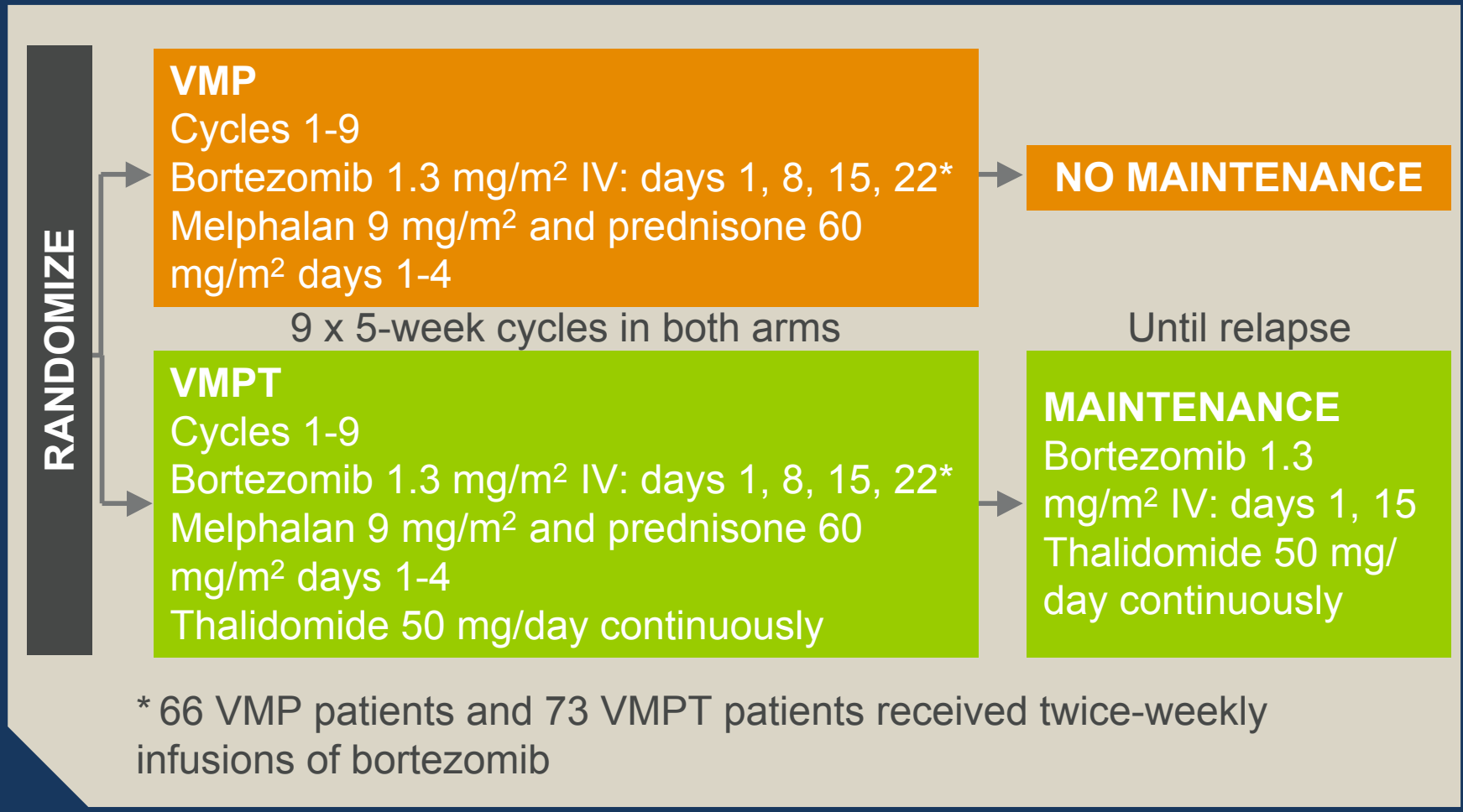
DR ZONDER: This study investigated the benefits and importance of: (1) sequenced drugs such as melphalan, (2) simultaneous treatment with bortezomib and thalidomide and (3) the inclusion of maintenance therapy in the treatment regimen. The study demonstrated that the 2 induction treatment regimens induced a higher response rate than that previously observed with TD in the same patient population. Therefore, either VMP or VTP would be considered as reasonable alternatives to TD therapy. However, VTP produced more toxic effects than VMP.

DR WOLF: This is an important study because of the elderly population evaluated. My take-home message from this study is that continued therapy with bortezomib is effective and a reasonable consideration.

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.

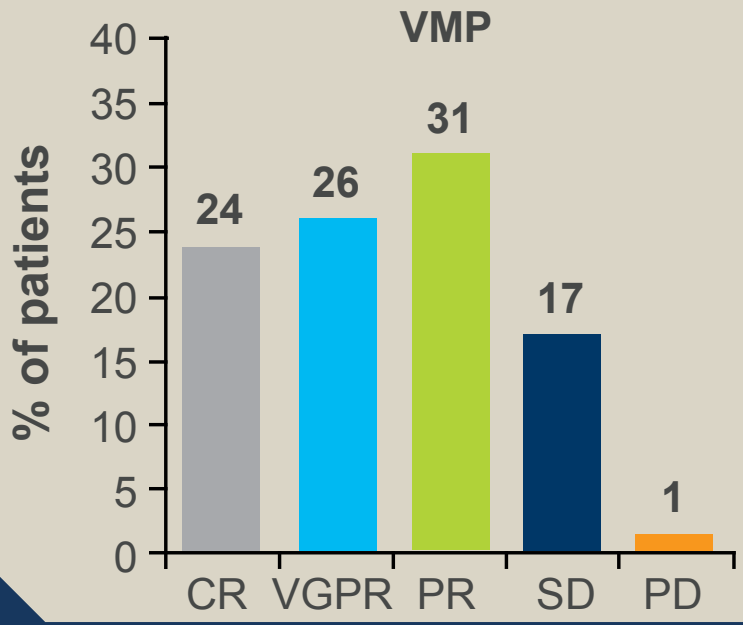
Study Schema

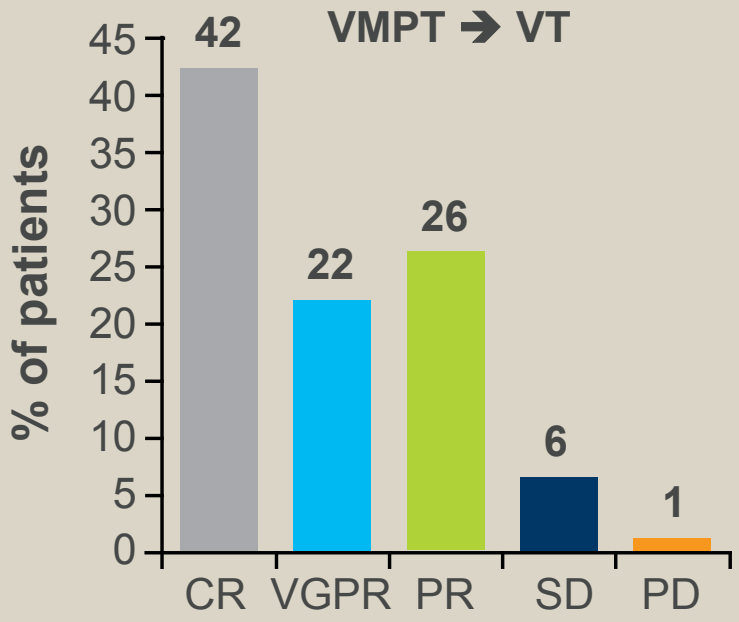


Palumbo A et al. *Proc ASH* 2010;Abstract 620.

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





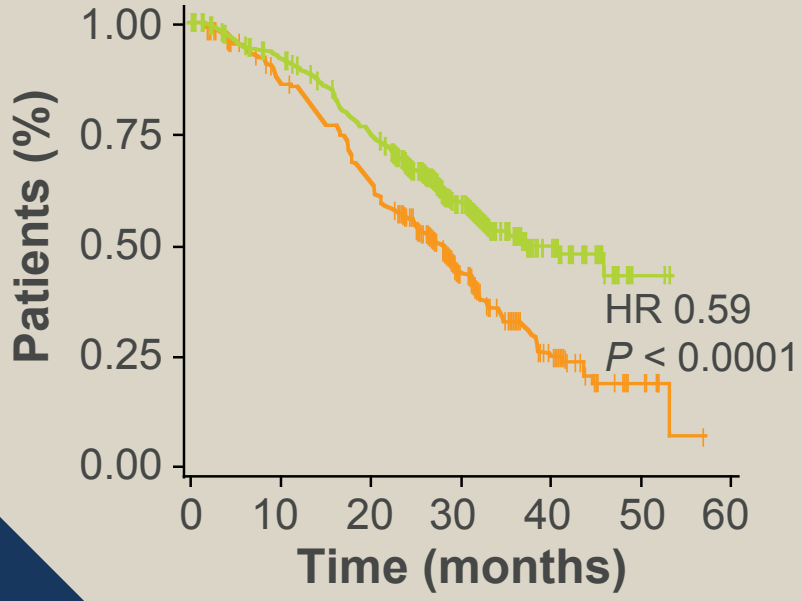
With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Results: Progression-Free Survival and Time to Next Therapy

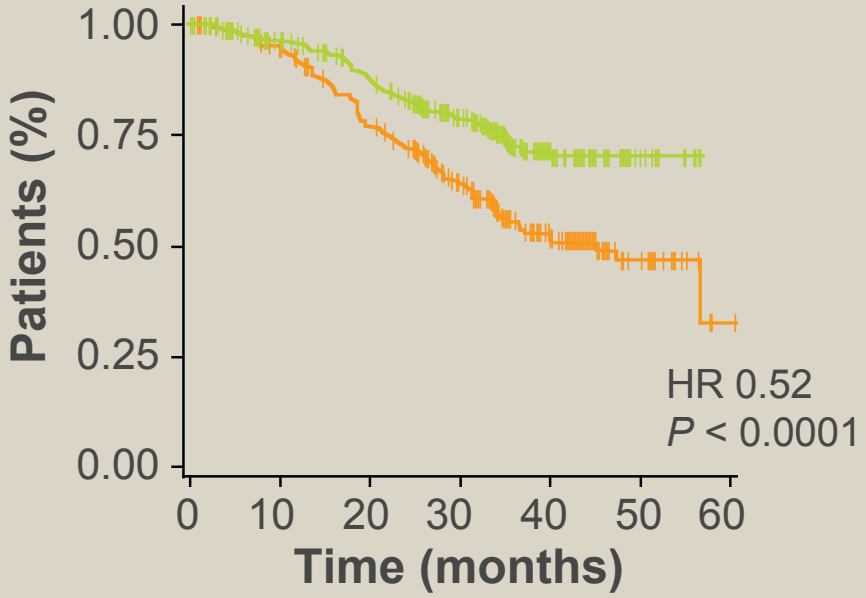
	3-years PFS	Median PFS
VMPT	51%	37.2 months
VMP	32%	27.4 months

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

Progression-Free Survival (PFS)
41% Reduced Risk of Progression

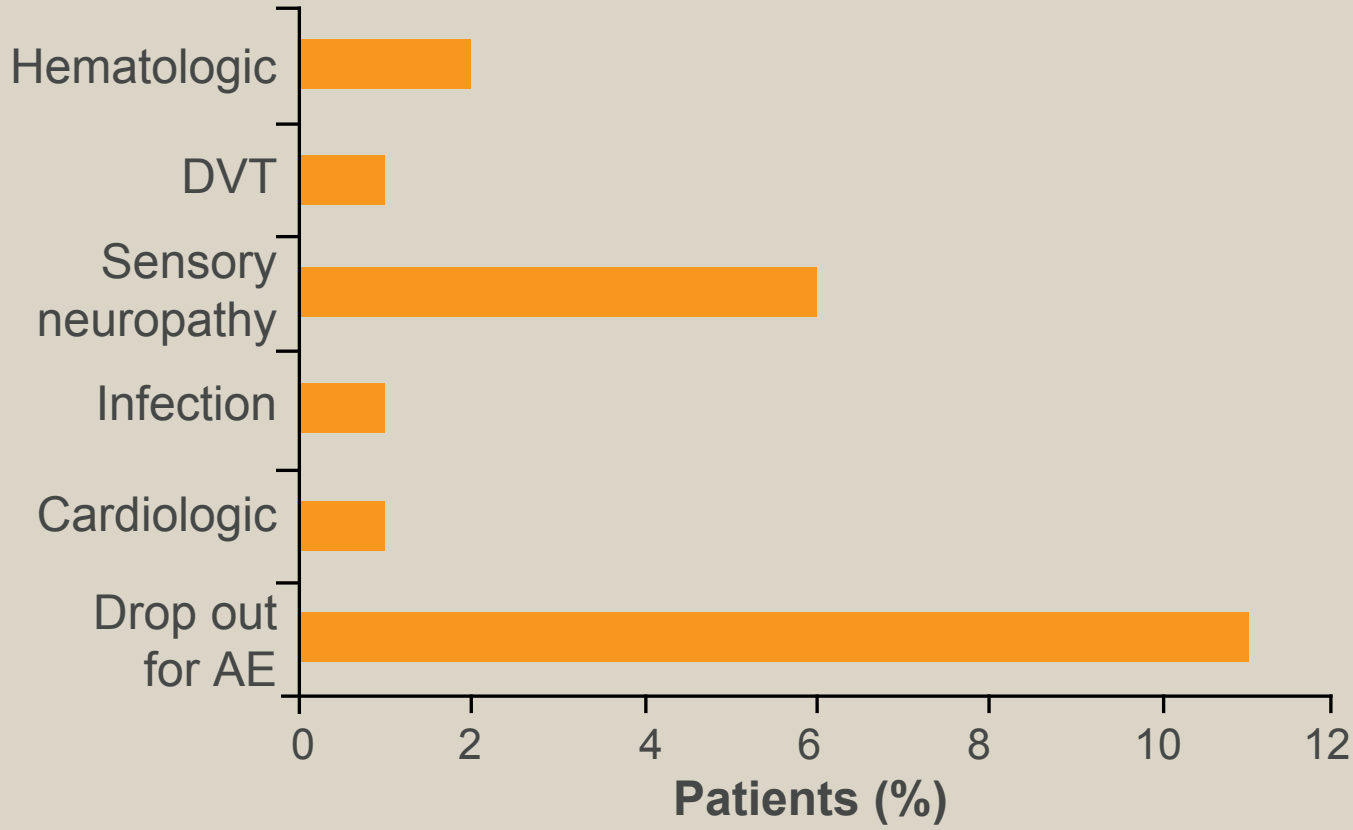


Time to Next Therapy (TNT)
48% Reduced Risk of Progression



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

Grade 3 or 4 Adverse Events (AEs) 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.

Efficacy and Toxicity by Bortezomib Schedule

	VMP twice weekly* (in VISTA)	VMP twice weekly	VMP once weekly
Complete response (CR)	30%	27%	23%
3-year progression-free survival (PFS)	NA	32%	35%
Sensory peripheral neuropathy (PN)			
Any grade	44%	43%	21%
Grade 3 or 4	13%	14%	2%
PN discontinuation	NA	16%	4%

* Mateos MV et al. *J Clin Oncol* 2010;28(13):2259-66.
NA = not applicable

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

Author Conclusions

- Statistically significant improvements reported with VMPT ➔ VT versus VMP for the treatment of newly diagnosed multiple myeloma.
  - CR rate: 42% versus 24% ($p < 0.0001$)
  - Median PFS: 37 months versus 27 months ($p < 0.0001$)
- VMPT ➔ VT prolonged PFS with an unprecedented 3-year PFS of 51% in elderly patients.
- Higher dose-intensity regimens seemed to be less effective in frail patients (≥75 years) (data not shown).
- Maintenance therapy with VT further improved PFS with a good safety profile.

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

Faculty Comments

DR ZONDER: The take-home messages in this study are (1) VMPT had a statistically significant and clinically somewhat significant increase in the overall response rate and (2) I believe the most impressive difference between these arms was the percent of deep responses and the PFS. The PFS benefit has everything to do with maintenance therapy.

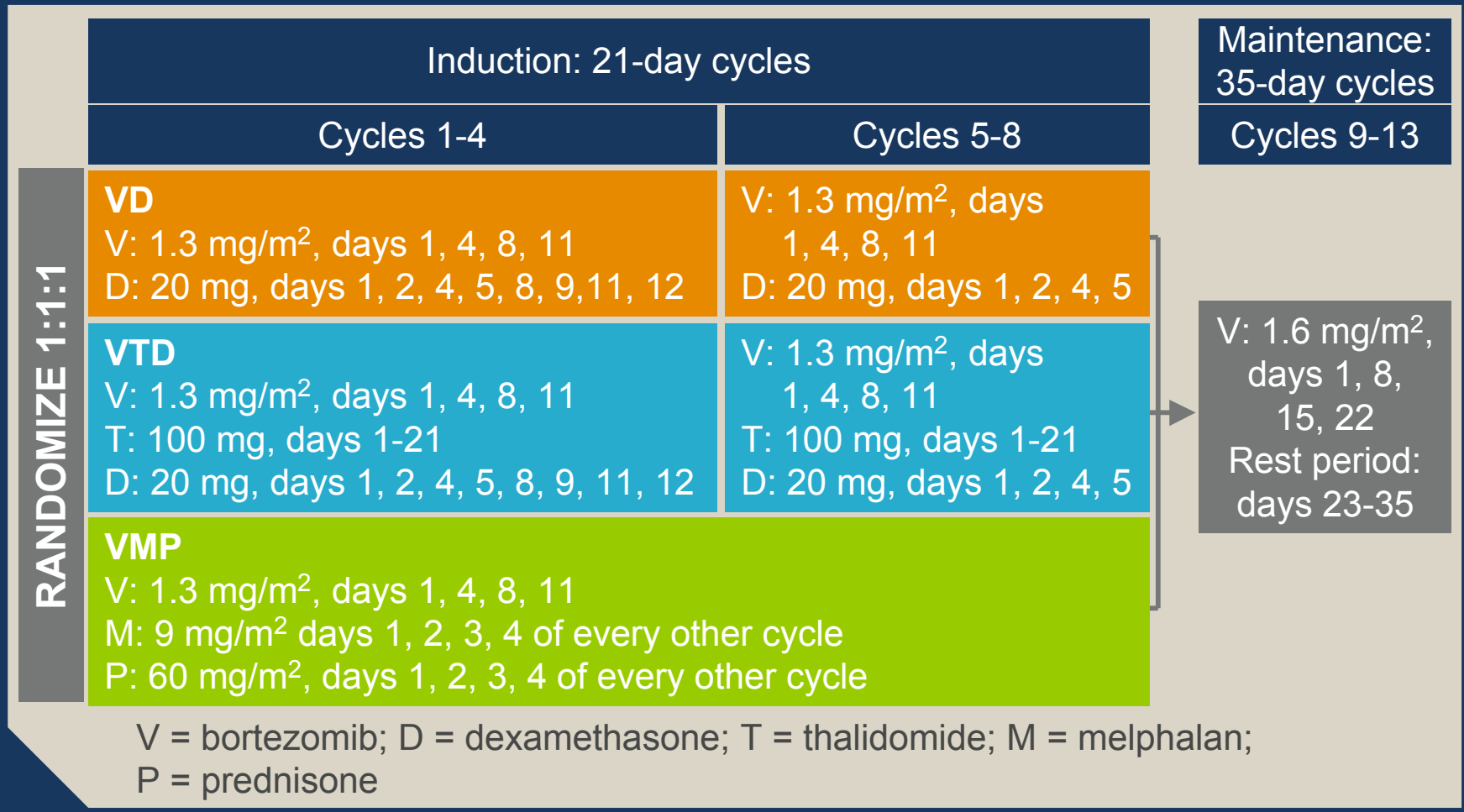
DR WOLF: Probably the most important aspect of this study wasn't planned initially. Some patients on this trial were switched from twice-weekly to once-weekly bortezomib. The important observation here is that in both groups, the once-weekly infusion reduced the incidence of severe peripheral neuropathy from 4% to 2%, which is huge.

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



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

Study Design

- Key inclusion criteria:
- Patients ≥18 years with previously untreated symptomatic multiple myeloma
- Karnofsky performance status score ≥50%
- Measurable disease requiring systemic therapy
- Key exclusion criterion:
- Grade ≥2 peripheral neuropathy (PN) within 21 days prior to enrollment
- Concomitant prophylaxis:
- VTD arm: Aspirin, full-dose warfarin or low molecular weight heparin unless medically contraindicated
- All groups: Prophylaxis for herpes zoster recommended

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

Efficacy: Survival and Response Rates

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

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%

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

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

Treatment Emergent Grade ≥3 Adverse Events (AEs)

	VD		VTD		VMP	
	I (n = 99)	M (n = 55)	I (n = 93)	M (n = 31)	I (n = 99)	M (n = 43)
At least 1 Grade ≥3 AE	70%	7%	84%	6%	79%	2%
PN	15%	5%	26%	6%	20%	2%
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.

Peripheral Neuropathy

	VD (n = 99)		VTD (n = 93)		VMP (n = 99)	
	I (n = 99)	M (n = 55)	I (n = 93)	M (n = 31)	I (n = 99)	M (n = 43)
Any grade PN resulting in dis-continuation of all study drugs	7%	4%	18%	0%	18%	0%
Grade ≥3 PN resulting in dis-continuation of all study drugs	4%	4%	13%	0%	14%	0%
Median time to PN	77 days		41 days		63 days	

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

Author Conclusions

- All 3 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 on the VTD arm.
- Single-agent bortezomib maintenance therapy after induction resulted in some increase of ≥VGPR rates in all 3 arms and was well tolerated.
  - Compared to postinduction rates, the rates of all-grade and Grade ≥3 PN did not increase substantially in any of the 3 treatment arms.
- PFS appeared similar among the treatment arms in the intent-to-treat population.

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

Faculty Comments

DR ZONDER: This study evaluated VD versus VTP versus VMP followed by 25 weeks of weekly maintenance bortezomib in all arms. All 3 bortezomib-based regimens resulted in substantial efficacy after 8 cycles. Overall response rates were 68% (VD), 78% (VTP) and 71% (VMP). Response rates were comparable (increased 1% to 3%) after bortezomib maintenance, but I don't believe that's all that surprising.

DR WOLF: The take-home message in this study is that 3-drug regimens are marginally better than 2-drug regimens, and you can continue bortezomib weekly. Response rates improved after bortezomib maintenance, with no increase in the incidence of peripheral neuropathy.

The Efficacy and Safety of Lenalidomide and Dexamethasone in Relapsed and/or Refractory Multiple Myeloma Patients with Impaired Renal Function

Dimopoulos M et al.
Cancer 2010;116(16):3807-14.

Introduction

- 20% of patients with multiple myeloma (MM) present with renal failure[1], which is the second most common cause of death in patients with MM[2] ([1] *Leukemia* 2008;22:1485, [2] *Arch Pathol Lab Med* 2004;128:875).
- Recovery of renal function can occur through therapeutic control of MM and is associated with an improvement in outcome (*Arch Intern Med* 1998;158:1889).
- Lenalidomide (LEN) with dexamethasone (DEX) is an effective therapy for MM associated with an overall response rate of 60% (*N Engl J Med* 2007;357:2133).
- Current study objective:
  - Assess the effect of renal dysfunction on safety and efficacy outcomes of patients treated with lenalidomide

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Study Methods

- Retrospective analysis of 350 patients randomly assigned to receive LEN with DEX in MM-009 and MM-010 Phase III trials
- Renal function was assessed throughout the study by measurement of serum creatinine levels and calculation of creatinine clearance (CL_{cr}).
- CL_{cr} values were used to subdivide patients into renal impairment (RI) subgroups
  - Mild or no RI = CL_{cr} ≥60 mL/minute
  - Moderate RI = CL_{cr} ≥30 mL/minute and <60 mL/minute
  - Severe RI = CL_{cr} <30 mL/minute

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Efficacy Outcomes According to Renal Function

Clinical parameter	Mild or no RI (n = 243)	Moderate RI (n = 82)	Severe RI (n = 16)
Overall response	64%	56%	50%
Complete response	16%	16%	6%
Very good partial response	19%	11%	31%
Partial response	30%	29%	13%
Median time to progression	12.0 mo	11.1 mo	7.8 mo
Median progression-free survival	11.1 mo	9.5 mo	7.8 mo
Median overall survival	38.9 mo	29.0 mo*	18.4 mo*

* Includes “response was not evaluable” patients and those without response assessment; $p = 0.006$ versus mild or no RI

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Dosage Information According to Renal Function

Variable	Mild or no RI (n = 243)	Moderate RI (n = 82)	Severe RI (n = 16)
Median LEN dose	25 mg/d	25 mg/d	15 mg/d*
Dose reduction/interruption due to adverse event	22%	40%*	38%*
Median time to LEN dose reduction	99 days	85 days	78 days
Discontinuation due to adverse event	12%	18%	38%*

* $p < 0.05$ versus patients with mild or no RI

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Recommendations for LEN Dosing in Patients with MM and Renal Impairment*

Category	Renal function†	LEN dosing in MM
Moderate RI	CL_{cr} ≥30mL/min to <60 mL/min	10 mg every 24 h
Severe RI	CL_{cr} <30 mL/min (not requiring dialysis)	15 mg every 48 h
End-stage renal disease	CL_{cr} <30 mL/min (requiring dialysis)	5 mg once daily; on dialysis days, dose administered after dialysis

* Based on LEN prescribing information
† Cockcroft-Gault CL_{cr}

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Author Conclusions

- With careful monitoring of the CL_{cr} level and adverse events and undertaking the appropriate dose adjustments, LEN with DEX is an effective and well-tolerated treatment option for patients with MM and RI.
- Patients with moderate to severe RI:
  - Had increased incidence of thrombocytopenia (data not shown)
  - Required more frequent LEN dose reduction/interruption
  - Had shorter overall survival
- Formal studies confirming the efficacy of LEN in patients with renal failure are warranted and ongoing.
- For future studies of LEN, it is important to convert serum creatinine to CL_{cr} and to use CL_{cr} for recommended LEN dosage adjustments for patients with RI.

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Faculty Comments

DR BENSINGER: Compared to patients with mild or no renal dysfunction, patients with moderate to severe renal dysfunction did not live as long and their disease progressed faster. With the proper dose adjustments, this study demonstrated that lenalidomide was safe and effective for patients with renal impairment. I had a patient with multiple myeloma who developed rapidly progressive renal failure. We were able to improve his renal function and bring him back into remission using low-dose lenalidomide at 5 mg, followed by 10 mg.

DR WOLF: The message here is that you can use lenalidomide in this setting. If I opt to do so, I start at a low dose. If the patient's counts are fine, I'll raise the dose. You have to be careful and you have to adjust your dose.