5 Minute JournalClub

Key ASH Presentations

Issue 1, 2011

Lenalidomide Maintenance for Patients with Newly Diagnosed Multiple Myeloma (MM) or MM in the Post-Transplant Setting

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

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.

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To go directly to slides and commentary, **click here**.

One can make the argument that the past few years have seen more important new agents, regimens and trial reports in multiple myeloma than any other corner of oncology, including breast cancer. At last month's ASH meeting in Orlando, we once again saw a staggering array of presentations and posters that both shed light on and add complexity to the management of this fascinating disease. In this, the first of nine brief ASH "highlight reels," we capsulize a number of key papers related to up-front treatment of multiple myeloma:

1. **The new "RVD"?**
Three years after Paul Richardson's landmark presentation of unprecedented outcomes for induction with lenalidomide, bortezomib and dexamethasone (RVD), Andrzej Jakubowiak wowed the masses in Orlando with results of a Phase I/II study of the irreversible proteasome inhibitor carfilzomib in combination with len and dex. These early efficacy data look a lot like what had been previously seen with RVD (100 percent response rate, 63 percent ≥VGPR) but with essentially no peripheral neuropathy. Stay tuned.

2. **Lenalidomide maintenance continues to impress.**
In an important trend related to the benefits of more prolonged treatment, further follow-up of the IFM trial first presented at ASCO continues to demonstrate an important advantage to maintenance len after transplant. A related paper by Antonio Palumbo — in the nontransplant setting — in which len maintenance was used after induction with melphalan/lenalidomide/prednisone also showed favorable results.

3. **Longer-term bortezomib in the up-front setting appears safe and effective in older patients.**
The UPFRONT trial showed impressive efficacy and acceptable neurotoxicity when weekly maintenance bortezomib was utilized after bortezomib-based initial induction regimens. Another paper by Palumbo also reported high response rates with bortezomib/melphalan/prednisone/thalidomide (VMPT) followed by weekly maintenance bortezomib/thalidomide (VT). As has been previously reported, neurotoxicity was reduced significantly when weekly as opposed to biweekly bortezomib was utilized.

4. **More data support low-dose dex with lenalidomide induction (Rd).**
A new analysis from the landmark ECOG trial clearly demonstrates that even in younger patients, lower-dose dex results in better outcomes.

Finally, we can happily report that the increasingly complex treatment algorithms for myeloma are being successfully implemented in daily practice. A **cross-sectional case survey of patients treated in a community setting in the last two years** reported as a poster by our CME group at the ASH meeting demonstrates consistently high response rates with modest toxicities in patients older and younger than age 75.

This Friday we will welcome eight noted clinical researchers to our recording studio in Miami for our third annual NHL/CLL Think Tank, and for the next issue of this series we'll provide you with their thoughts on ASH, including perspectives on the long-awaited findings from the Intergroup trial comparing rituximab monotherapy to "watch and wait."

Neil Love, MD
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Lenalidomide Maintenance for Patients with Newly Diagnosed Multiple Myeloma (MM) or MM in the Post-Transplant Setting

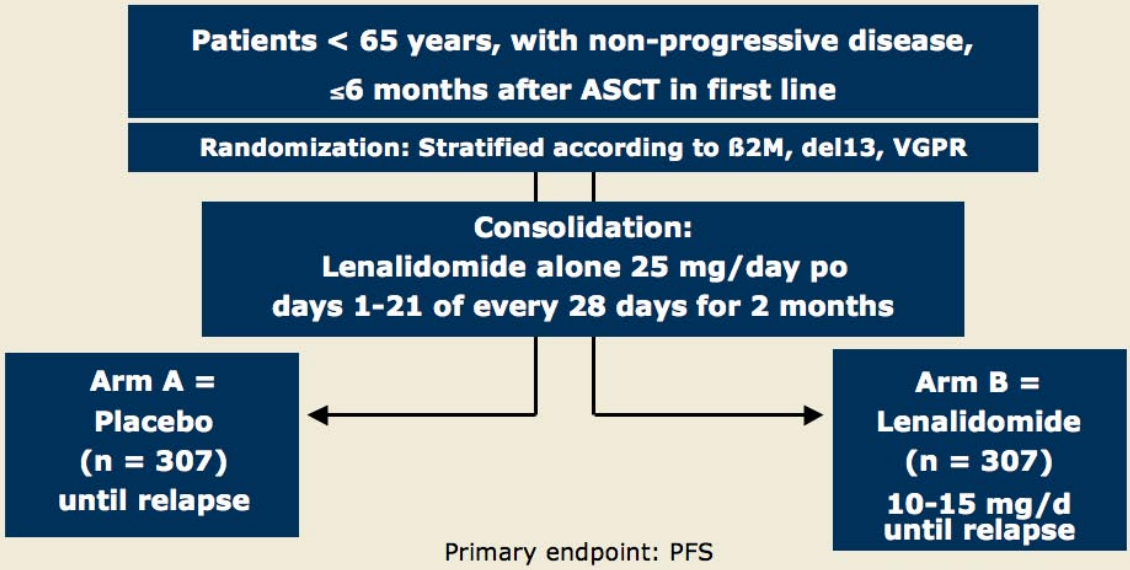
Presentations discussed in this issue

Attal M et al. **Maintenance treatment with lenalidomide after transplantation for MYELOMA: Final analysis of the IFM 2005-02.** *Proc ASH* 2010;**Abstract 310**.

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

Slides from presentations at ASH 2010 and transcribed comments from a recent interview with Rafael Fonseca, MD (12/22/10)

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.

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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.

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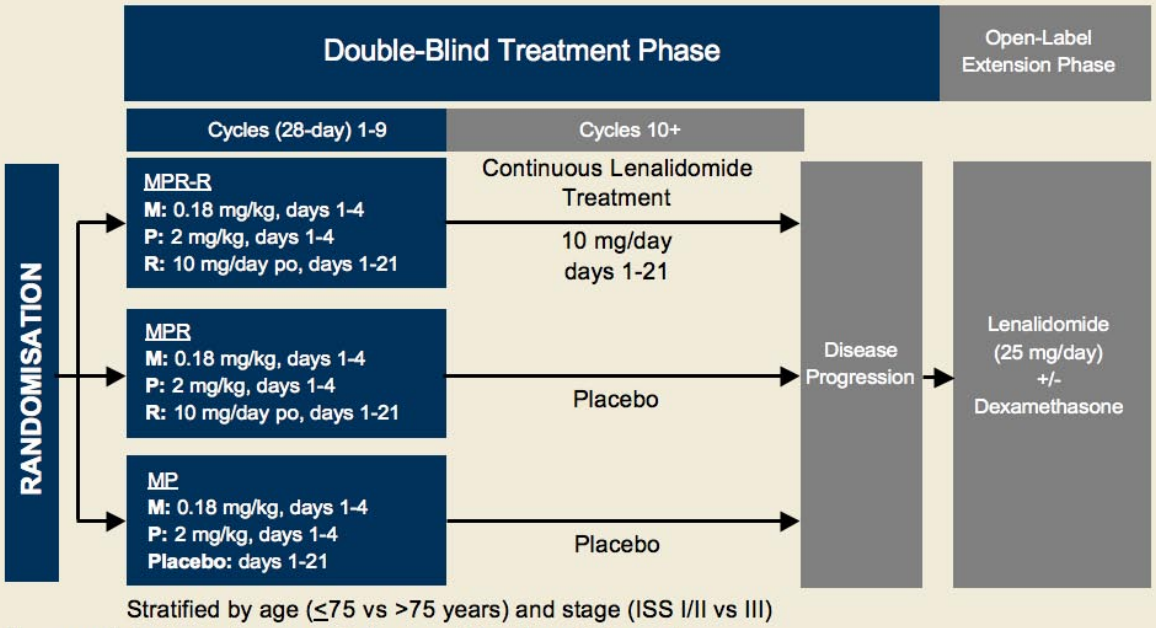
Phase III Study Schema



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.

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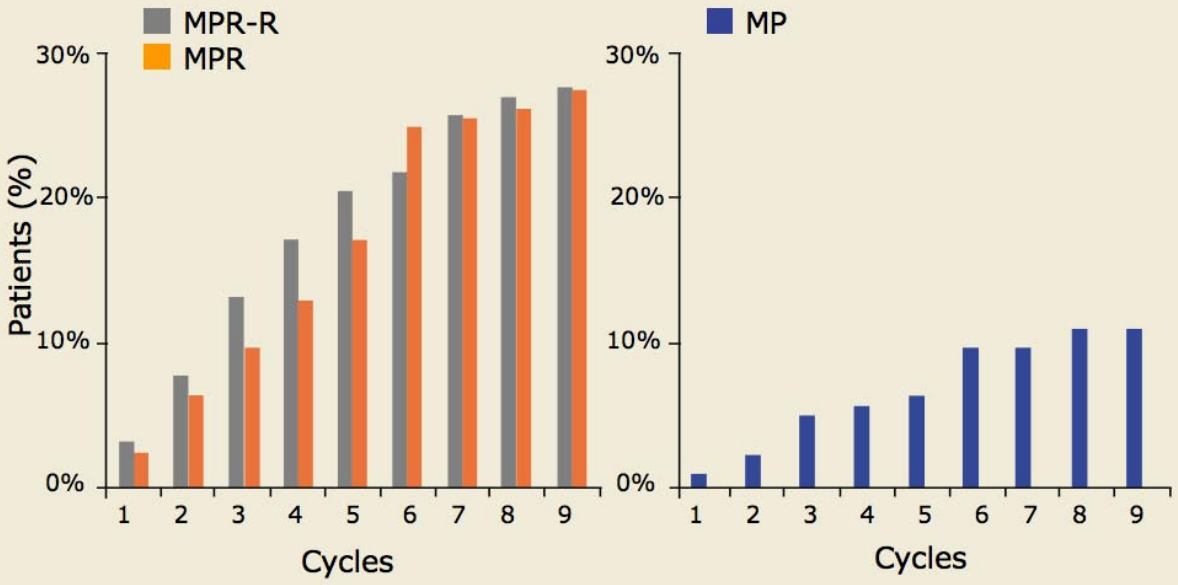
Response Rate



All patients achieved very good response rate or better.

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

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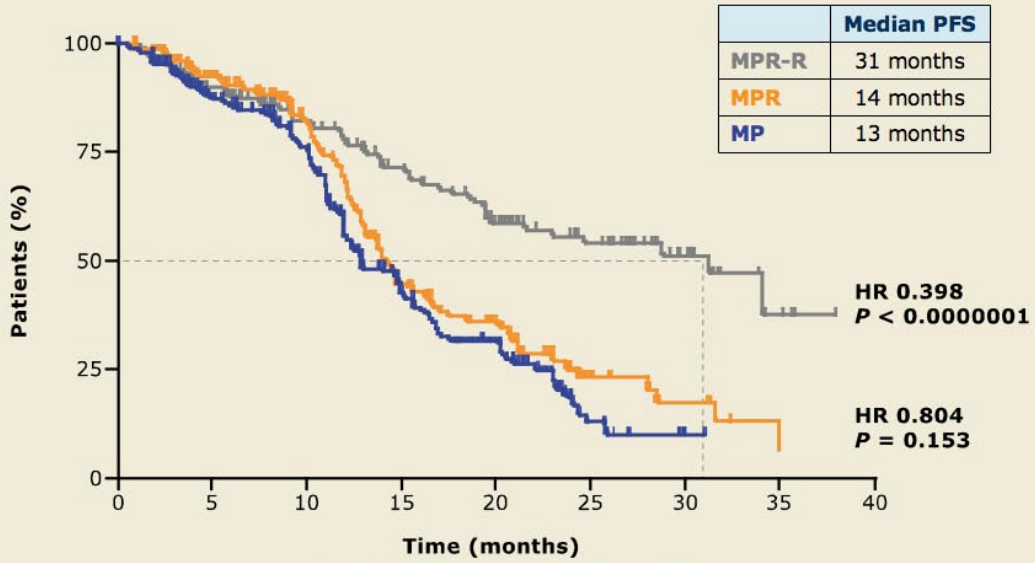
Progression-Free Survival (PFS)*
All Patients



	Median PFS
MPR-R	31 months
MPR	14 months
MP	13 months

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.

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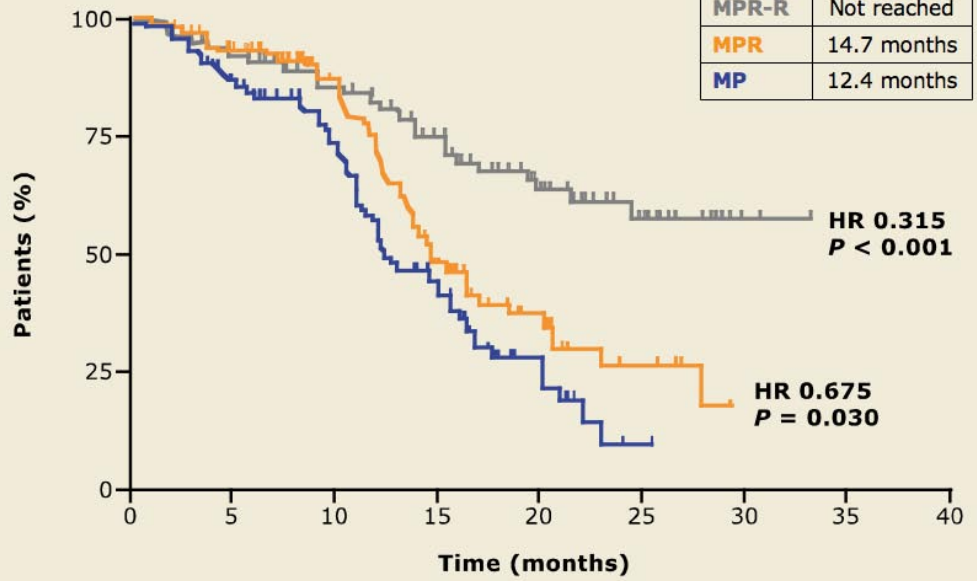
Progression-Free Survival (PFS)
Patients Age 65-75 Years



	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.

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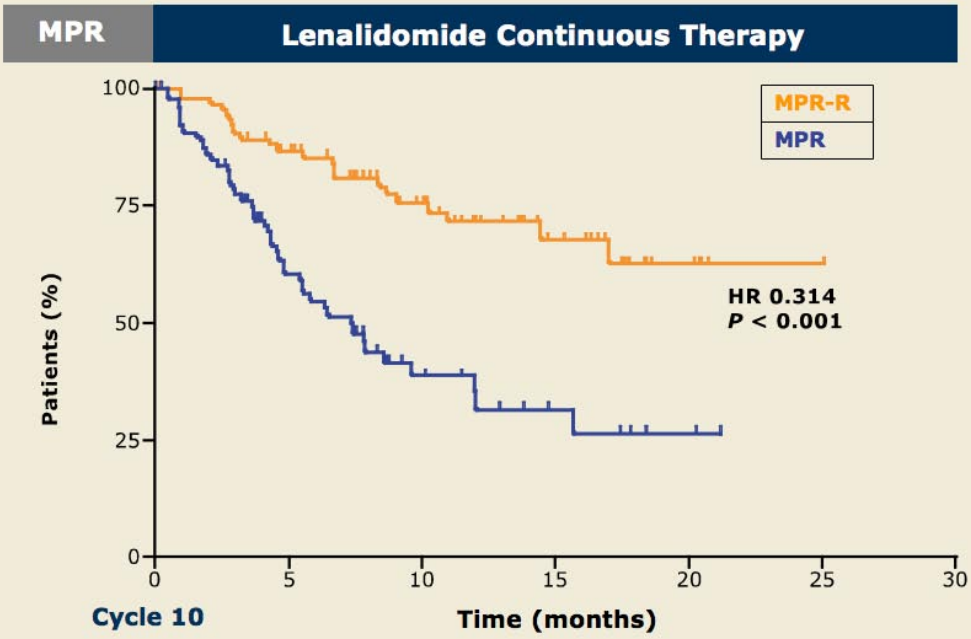
Landmark Analysis



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

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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.

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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.

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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

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