5 Minute JournalClub

Key ASH Presentations
Issue 7, 2012

Lenalidomide Maintenance After Lenalidomide/Melphalan/ Prednisone for Elderly Patients with Newly Diagnosed MM

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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 and new information 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, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Integrate emerging research information on the use of proteasome inhibitors and immunomodulatory agents to individualize induction treatment recommendations and maintenance therapeutic approaches for elderly patients with multiple myeloma.
- Compare and contrast the benefits and risks of lenalidomide- and bortezomib-based induction therapy, and consider the role of combined immunomodulatory and proteasome-inhibitor regimens for elderly patients with multiple myeloma.
- Communicate the benefits and risks of postinduction maintenance therapy with lenalidomide- and bortezomib-based therapies to elderly patients with multiple myeloma.
- Weigh the benefit of continuous therapy with lenalidomide against the risk of development of second primary cancer for patients who receive lenalidomide with alkylating agents.

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

In ancient oncology days, laboratory scientists like Drs Howard Skipper and Frank Schabel created a kinetically defined portrait of cancer that was most amenable to a "shock and awe" therapeutic strategy involving short-term chemo and indirectly led to the use of supportive transplants. This "MTD" approach has gradually given way to a new model in which more tolerable, targeted antitumor agents are utilized in doses and schedules that allow for prolonged administration. Of course the prototype for chronic anticancer treatment is imatinib in CML, but rituximab maintenance in indolent lymphoma and endocrine and anti-HER2 therapy in breast cancer are related examples, and our last email reflected on the apparent advantages to the prolonged use of bevacizumab and/or pemetrexed in nonsquamous cell lung cancer. In multiple myeloma a similar type of strategy has been increasingly discussed by investigators including Dr Antonio Palumbo, who was the first author on a related European Myeloma Network (EMN) report in the October issue of *Blood* titled "Personalized therapy in multiple myeloma according to patient age and vulnerability."

Side note: Make the experts sweat!

In less than 3 weeks (Friday, April 13th) myeloma investigators Drs Rafael Fonseca, Ravi Vij, Jeff Wolf and Jeff Zonder will join us in Miami to help create a new case-based audio program. As part of the project, we have reserved time to discuss cases and questions from the community at large. To that end, we encourage you to **visit our Facebook page** and post a case or **tweet us a question**. We will do our best to present these and follow up with the answers.

Dr Palumbo's concept — which he first presented to our audiences during an audio interview almost 2 years ago — centers on the notion that although MM is primarily a disease of older people (a third are over 75), the important improvement in survival observed in recent years from the introduction of IMiDs and proteasome inhibitors has been confined to patients under 70. As such, he has championed a new approach to treatment for older patients in which careful attention to the selection of regimen, dose, schedule and methods of administration allows for safe prolonged treatment and much better outcomes. In this issue of our program we review 5 important ASH papers, all of which directly or indirectly support this chronic disease model:

1. Continuous lenalidomide

Dr Palumbo presented a **follow-up analysis from his landmark European trial evaluating len maintenance** until and, in some cases, beyond disease progression in nontransplant-eligible patients receiving induction with either MPR or MP. The trial had previously demonstrated more than a doubling of PFS in favor of maintenance in both induction arms, and this report — which divided the results by age — found similar benefits above and below age 75. Many investigators, including Dr Sagar Lonial, believe that avoiding

disease progression and the challenge of re-treatment is particularly important in patients older than age 75.

Dr Palumbo also presented **data at ASH on second primary cancers (SPC)** in 2,459 patients from 9 trials of the EMN. Prior studies have suggested an increased incidence of SPC (particularly AML/MDS) in all patients with MM, and this post hoc analysis demonstrated a modest increased SPC risk for patients on len maintenance, particularly those who had also received melphalan-based therapy. The report concludes that the risk of SPC is much smaller than the antimyeloma benefits of maintenance len.

2. UPFRONT study: Three different induction bortezomib-based regimens

In this Phase IIIb effort, VD, VTD and VMP induction were compared and although all 3 resulted in good tumor outcomes, VTD was found to be superior but also more toxic — particularly in terms of peripheral neuropathy. These findings suggest to some that the less toxic VD regimen may be a better option for the elderly, particularly if bortezomib can be administered weekly or subcutaneously.

3. VISTA

At ASH the final 5-year findings from this landmark Phase III trial continued to demonstrate an overall survival benefit (13.3 months) associated with the addition of bortezomib to melphalan/prednisone. With perhaps the longest follow-up reported in the era of novel agents, this study supports the concept that early treatment can profoundly affect the longer-term natural history of the disease.

4. Spanish study of maintenance with an IMiD and a proteasome inhibitor

This update presented by Dr Maria-Victoria Mateos revealed that both VT and VP maintenance after induction resulted in better outcomes with a trend favoring VT. The natural extension of this multiagent maintenance strategy is embodied in an ongoing Dana-Farber study of "RVD lite" in older patients that allows for long-term treatment by incorporating lower doses and providing flexibility in terms of bortezomib administration.

Any questions about this? **Facebook us!**

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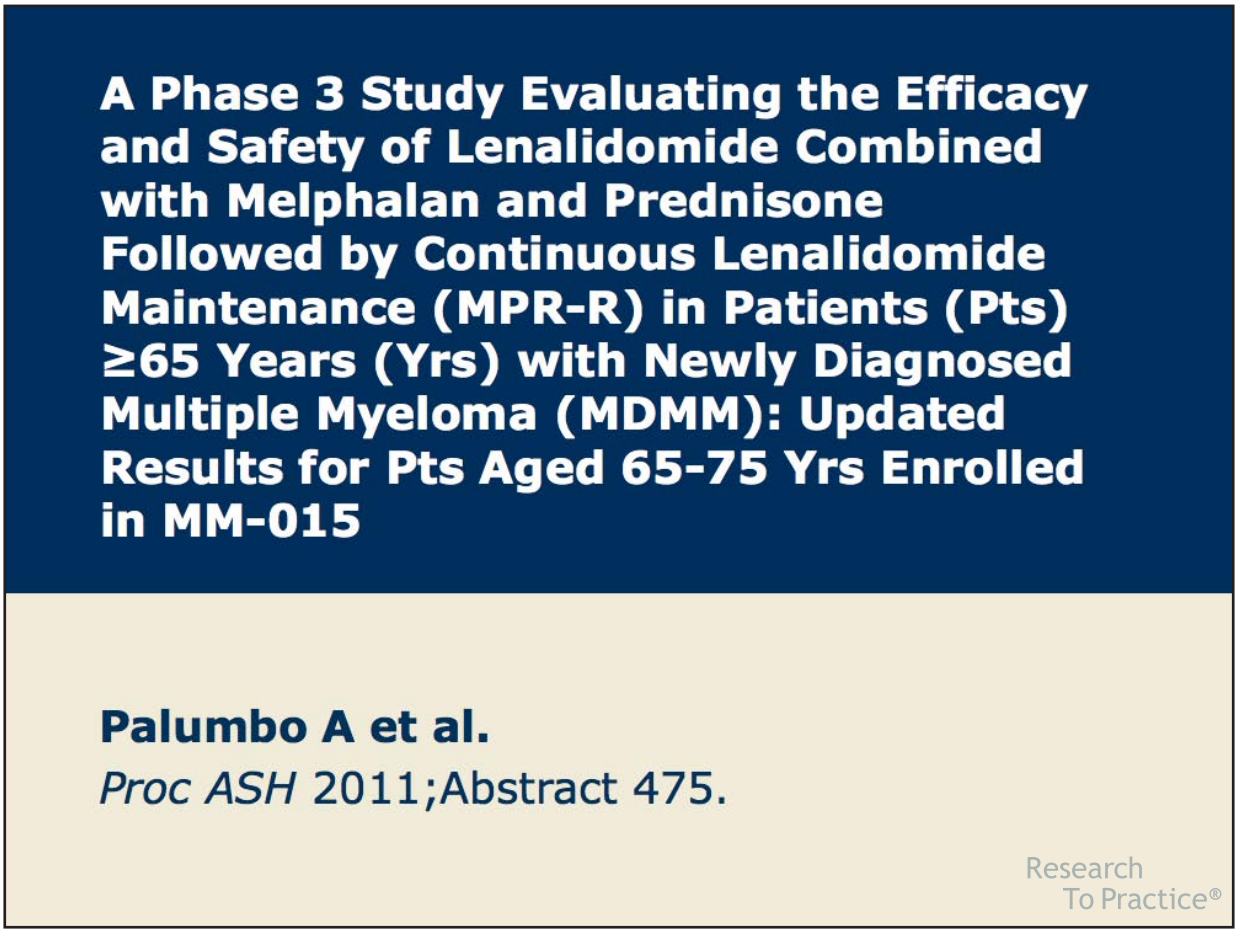
Lenalidomide Maintenance After Lenalidomide/Melphalan/ Prednisone for Elderly Patients with Newly Diagnosed MM

Presentation discussed in this issue

Palumbo A et al. **A Phase 3 study evaluating the efficacy and safety of lenalidomide (len) combined with melphalan and prednisone followed by continuous lenalidomide maintenance (MPR-R) in patients (pts) ≥ 65 years (yrs) with newly diagnosed multiple myeloma (NDMM): Updated results for pts aged 65-75 yrs enrolled in MM-015.** *Proc ASH* 2011;**Abstract 475**.

Slides from a presentation at ASH 2011 and transcribed comments from recent interviews with Sagar Lonial, MD (1/25/12) and Paul G Richardson, MD (1/24/12)



Background

- Interim results from the randomized placebo-controlled Phase III trial MM-015 showed unprecedented reduction in the risk of disease progression with induction melphalan (M), prednisone (P) and Len (R) followed by Len maintenance therapy (MPR-R) (*Proc ASH* 2010;Abstract 622).
  - Overall, MPR-R reduced the risk of disease progression by 58% compared to MP
- **Objective:**
  - Report updated efficacy and safety results with a focus on a subpopulation of elderly patients, aged 65 to 75 years, from the MM-015 trial.

Palumbo A et al. *Proc ASH* 2011;Abstract 475.

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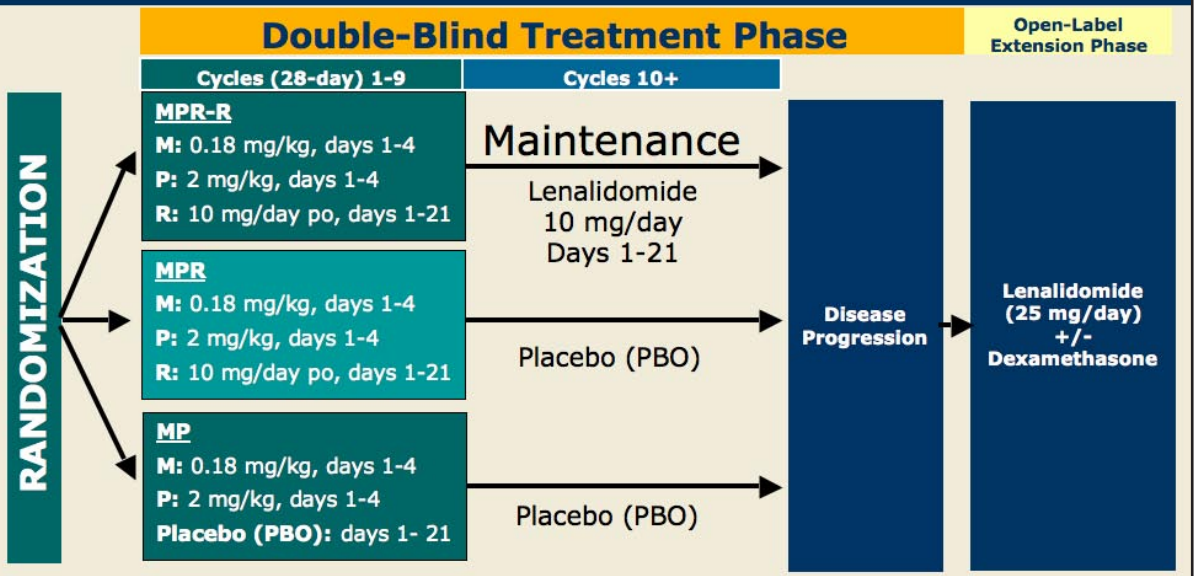
MM-015 Study Design (N = 459)



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

With permission from Palumbo A et al. *Proc ASH* 2011;Abstract 475.

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Second Primary Malignancies (SPMs) and Survival in All Patients

SPM, n (IR per 100 per year)	MPR-R (n = 150)	MPR (n = 152)	MP (n = 153)
Total invasive SPMs	12 (3.04)	10 (2.57)	4 (0.98)
Hematologic	7 (1.75)	6 (1.54)	1 (0.24)
Solid tumors	5 (1.26)	5 (1.28)	3 (0.74)
Nonmelanoma skin cancer	2 (0.50)	5 (1.29)	6 (1.50)
Survival	**MPR-R**	**MPR**	**MP**
Median PFS*	31 mo	14 mo	13 mo
Four-year OS rate	59%	58%	58%

IR = incidence rate; OS = overall survival

* Hazard ratio (HR) MPR-R vs MP: 0.395 ($p < 0.001$); HR MPR vs MP: 0.796 ($p = 0.135$)

Palumbo A et al. *Proc ASH* 2011;Abstract 475.

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Response Rates: Intention-to-Treat Population (65-75 Years)

Best response	MPR-R (n = 116)	MPR (n = 116)	MP (n = 116)
ORR	79.3%	73.3%	47.4%
≥VGPR	35.3%	35.3%	11.2%
PR	44.0%	37.9%	36.2%
SD	15.5%	23.3%	50.0%
PD	0	0.9%	0
NE	5.2%	2.6%	2.6%
Median time to response	2 mo	2 mo	3 mo

ORR = overall response rate; PR = partial response; VGPR = very good PR;
SD = stable disease; PD = progressive disease; NE = not evaluable

Palumbo A et al. *Proc ASH* 2011;Abstract 475.

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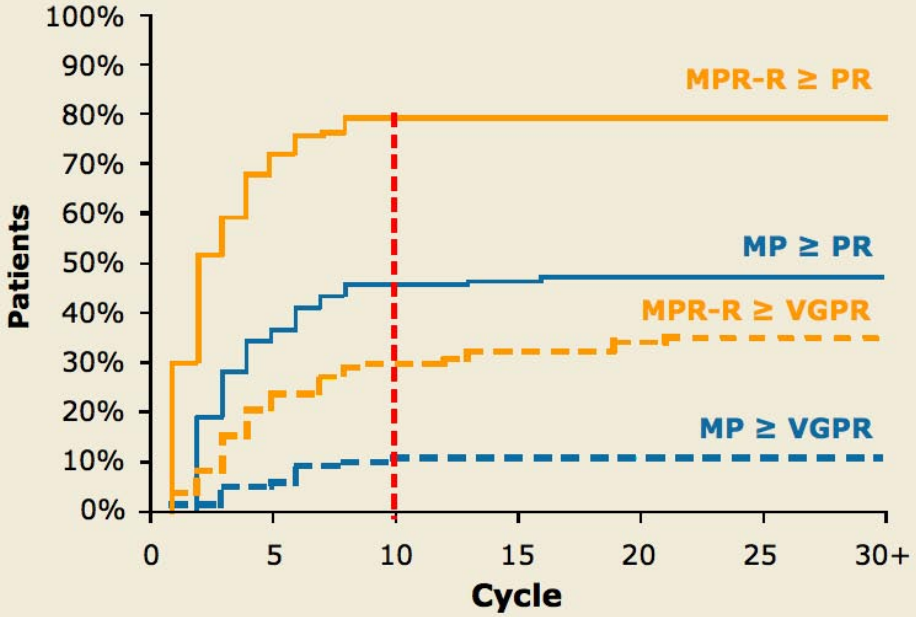
Time to ≥PR and ≥VGPR: MPR-R versus MP (65-75 Years)



With permission from Palumbo A et al. *Proc ASH* 2011;Abstract 475.

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PFS and OS (65-75 Years)

Survival	MPR-R	MPR	MP
Median PFS*	31 mo	15 mo	12 mo
4-year OS†	69%	61%	58%

* MPR-R vs MP: 0.301 ($p < 0.001$); HR MPR vs MP: 0.618 ($p = 0.006$)

† HR MPR-R vs MP: 0.706 ($p = 0.133$); HR MPR vs MP: 0.902 ($p = 0.639$)

- Preplanned landmark analysis of PFS from maintenance entry showed a greater reduction in the risk of disease progression with MPR-R versus MPR (HR: 0.349; $p < 0.001$).

Palumbo A et al. *Proc ASH* 2011;Abstract 475.

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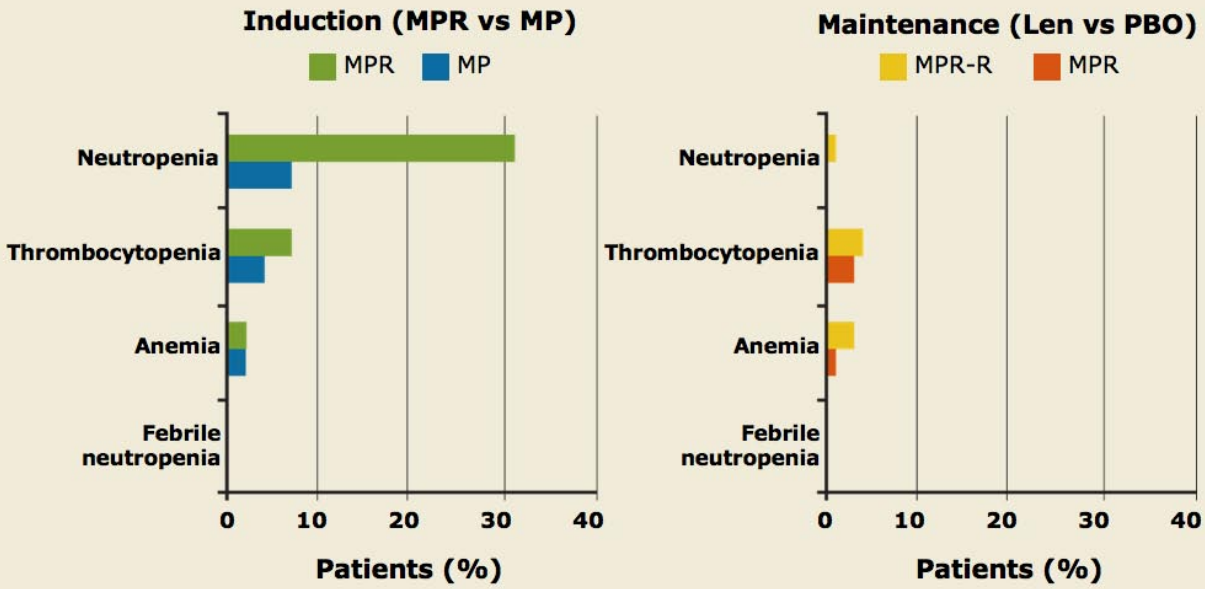
Grade 4 Hematologic Adverse Events (65-75 Years)



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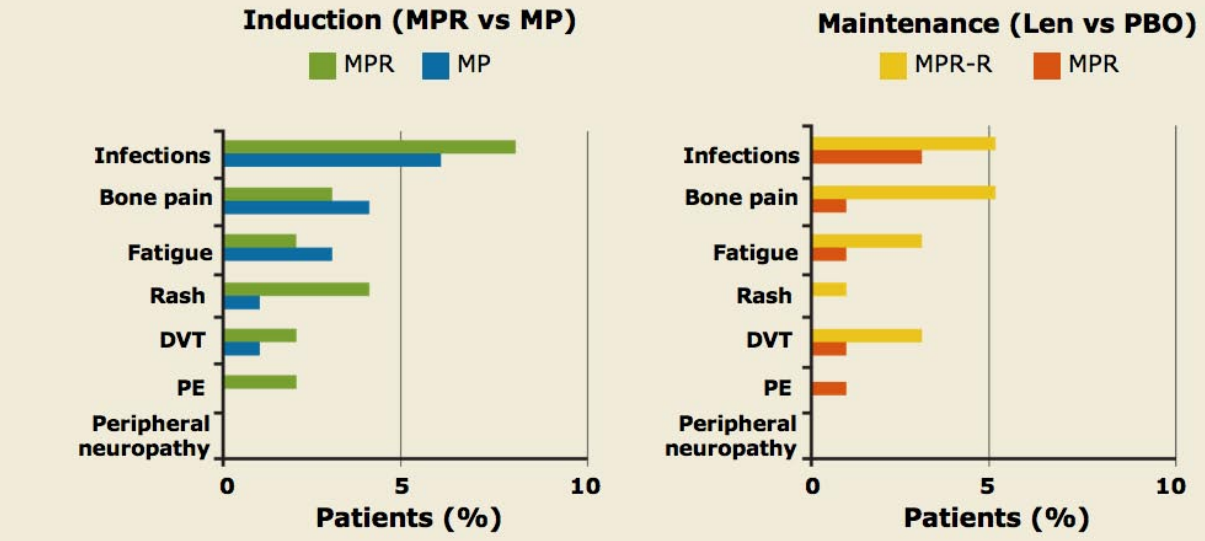
Grade 3/4 Nonhematologic Adverse Events (65-75 Years)



DVT = deep vein thrombosis; PE = pulmonary embolism

With permission from Palumbo A et al. *Proc ASH* 2011;Abstract 475.

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Author Conclusions

- Independent of age, lenalidomide maintenance reduced the risk of progression by 65% (hazard ratio: 0.34).
- Induction therapy with MPR reduced the risk of disease progression by 39% in patients aged 65-75 years with newly diagnosed MM (hazard ratio: 0.61).
- The continuous Len treatment with MPR-R in patients aged 65-75 years decreased the risk of disease progression by 70% (hazard ratio: 0.30).
- MPR-R treatment regimen demonstrated a trend toward a survival benefit in patients aged 65-75 years (hazard ratio: 0.70).

Palumbo A et al. *Proc ASH* 2011;Abstract 475.

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Investigator Commentary: Continuous Lenalidomide Treatment in Patients Age 65 to 75 with Newly Diagnosed Multiple Myeloma (NDMM)

This trial validates a continuous treatment approach in the studied patient population and clearly demonstrates a maintenance effect from Len. Although MPR improved PFS, greater benefit was observed with continuous Len treatment after induction therapy. In my view MPR is a challenging combination to use because it is associated with myelosuppression and forces the use of a lower Len dose. For example, even though the study administered a low dose of Len (10 mg/d) for induction and maintenance, I tend to use a higher Len range of 15 to 20 mg for my patients during induction therapy when I use other agents such as bortezomib. This notwithstanding, these data are exciting and clearly demonstrate that Len is important in elderly populations with NDMM.

Interview with Paul G Richardson, MD, January 24, 2012

This study clearly demonstrates that Len maintenance therapy has a major impact in terms of PFS in elderly patients with NDMM. However, whether MPR is better than MP is less clear. Maintenance therapy is important in elderly patients age 75 or older because there may not be a second chance for treatment if relapse occurs after stopping the initial therapy.

Interview with Sagar Lonial, MD, January 25, 2012