



Key ASH Presentations
Issue 7, 2012

UPFRONT Study of Bortezomib-Based Combinations 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.”

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

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.

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 IIb 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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UPFRONT Study of Bortezomib-Based Combinations for Elderly Patients with Newly Diagnosed MM

Presentation discussed in this issue

Niesvizky R et al. **Efficacy and safety of three bortezomib-based combinations in elderly, newly diagnosed multiple myeloma patients: Results from all randomized patients in the community-based, phase 3b UPFRONT study.** *Proc ASH 2011*; **Abstract 478**.

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

Efficacy and Safety of Three Bortezomib-Based Combinations in Elderly, Newly Diagnosed Multiple Myeloma Patients: Results from All Randomized Patients in the Community-Based, Phase 3b UPFRONT Study

Niesvizky R et al.

Proc ASH 2011; Abstract 478.

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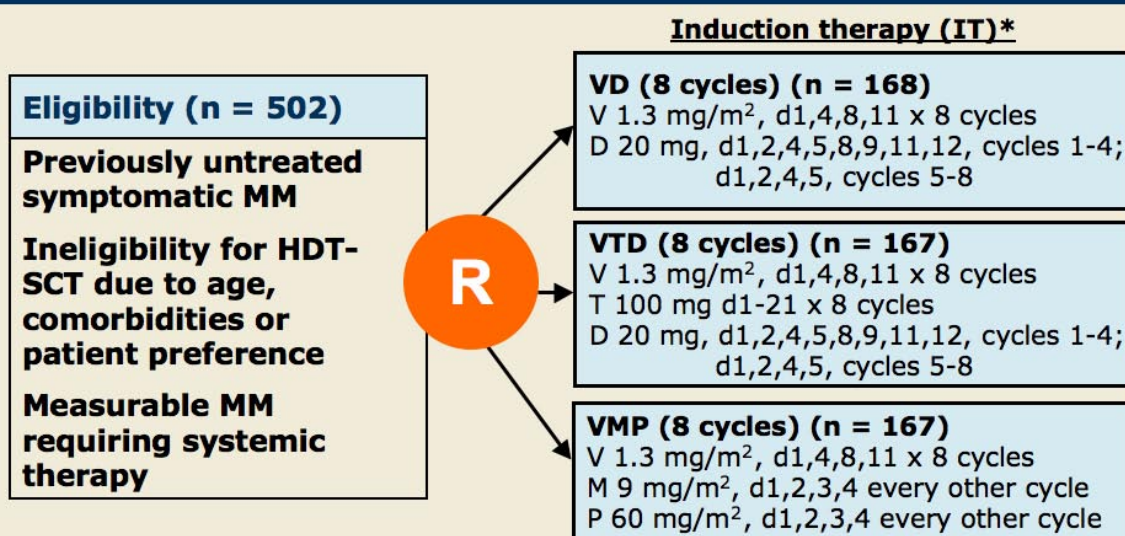
Background

- Often elderly patients with multiple myeloma (MM) are not eligible for high-dose therapy and stem cell transplant (HDT-SCT) because of age and comorbidities.
- Bortezomib-based therapies have demonstrated activity in patients with newly diagnosed MM in several Phase II and III trials (*JCO* 2010;28:4621; *Lancet* 2010;376:2075).
- However, the efficacy and safety of different bortezomib-based treatment regimens have not been directly compared.
- **Objective:**
 - Compare the efficacy and safety of bortezomib-based treatment regimens in patients with newly diagnosed MM who are not eligible for HDT-SCT, and evaluate its use as maintenance therapy.

Niesvizky R et al. *Proc ASH* 2011;Abstract 478.

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UPFRONT Trial Design



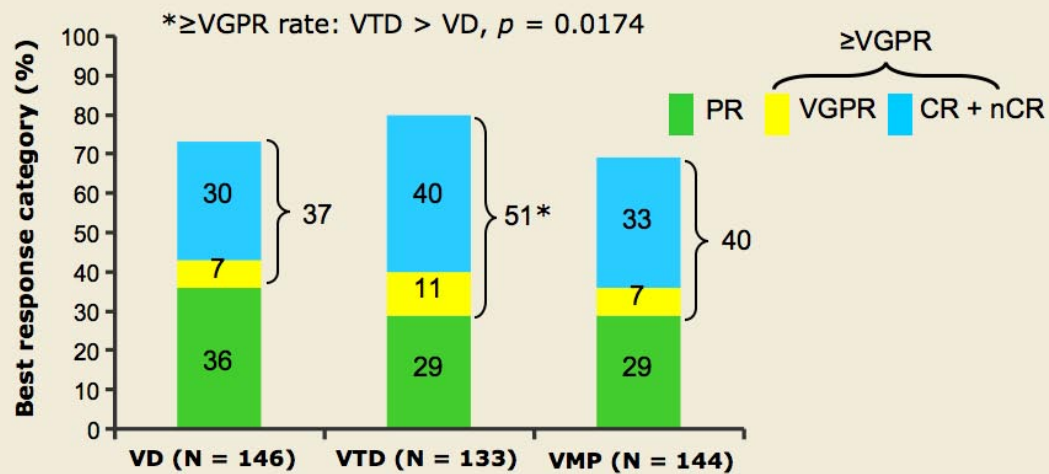
V = bortezomib; T = thalidomide; D = dexamethasone; M = melphalan; P = prednisone

* Followed by maintenance therapy (MT): V 1.6 mg/m², d1,8,15,22 x 5 cycles

Niesvizky R et al. *Proc ASH* 2011;Abstract 478.

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Best Confirmed Response Rates (RRs) During Induction and Maintenance

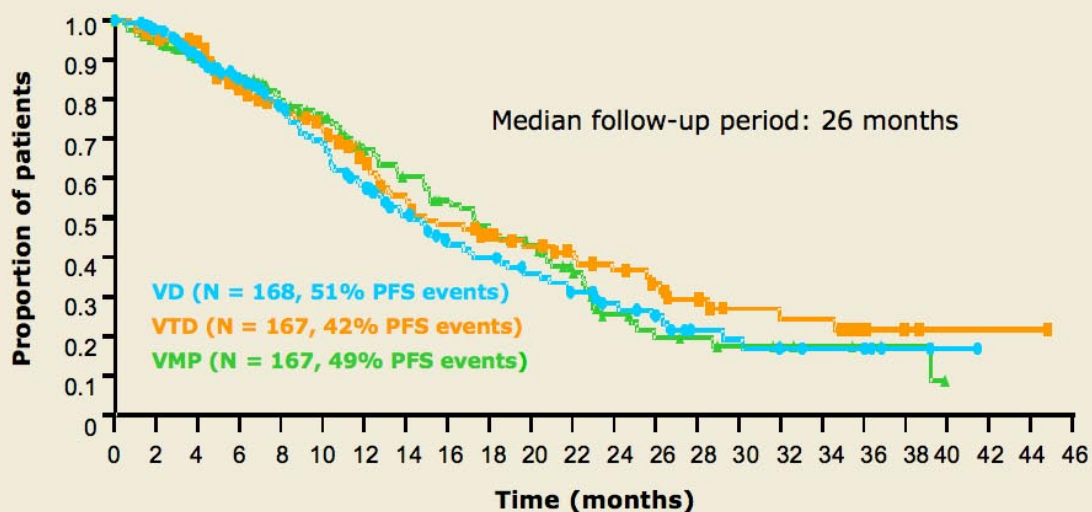


PR = partial response; VGPR = very good PR; CR = complete response; nCR = near CR

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Progression-Free Survival (PFS) in the Intention-to-Treat Population

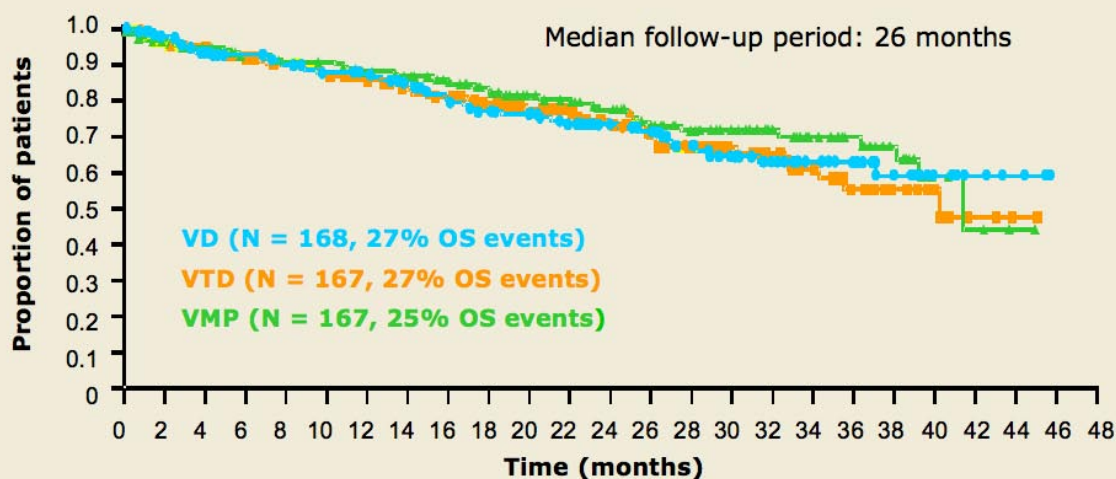


- 1-year PFS estimates (n = 502): 57.4% (VD), 63.8% (VTD), 67.3% (VMP)
- There were no statistically significant differences among treatment arms

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Overall Survival (OS) in the Intention-to-Treat Population



- 1-year OS estimates (n = 502): 87.4% (VD), 86.1% (VTD), 88.3% (VMP)
- 2-year OS estimates: 73.7% (VD), 73.6% (VTD), 77.6% (VMP)
- There were no statistically significant differences among treatment arms

With permission from Niesvizky R et al. *Proc ASH* 2011;Abstract 478.

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Selected Adverse Events (AEs)

Event	VD		VTD		VMP	
	IT (n = 165)	MT (n = 82)	IT (n = 158)	MT (n = 60)	IT (n = 163)	MT (n = 69)
At least 1 Grade ≥3 AE	74%	9%	84%	8%	82%	3%
PN	19%	6%	24%	7%	19%	3%
Fatigue	10%	2%	12%	0%	8%	0%
Diarrhea	9%	4%	3%	5%	7%	6%
Pneumonia	10%	1%	6%	0%	5%	3%
Neutropenia	2%	0%	3%	0%	18%	0%
≥1 serious AE	48%	11%	53%	12%	47%	9%
Discontinuation	29%		37%		34%	

IT = induction therapy; MT = maintenance therapy

Quality of life (QoL) trend: Poorer in VTD versus VD and VMP treatment arms

Niesvizky R et al. *Proc ASH* 2011;Abstract 478.

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Peripheral Neuropathy

	VD		VTD		VMP	
	IT (n = 165)	MT (n = 82)	IT (n = 158)	MT (n = 60)	IT (n = 163)	MT (n = 69)
Any grade PN	47%	6%	57%	7%	44%	4%
Grade ≥ 3 PN	19%	1%	24%	5%	19%	3%
Any grade causing discontinuation	10%	6%	16%	0%	17%	1%
Grade ≥ 3 PN causing discontinuation	7%	6%	12%	0%	13%	1%
Median time to PN onset	70 days		42 days		63 days	

IT = induction therapy; MT = maintenance therapy

Niesvizky R et al. *Proc ASH* 2011;Abstract 478.

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Author Conclusions

- VD, VTD and VMP were active in the treatment of elderly patients with newly diagnosed MM.
 - After MT, \geq VGPR rates were significantly higher for VTD than VD.
- PFS and OS appeared to be similar among the treatment arms in the intention-to-treat population at the studied follow-up period.
- The rates of Grade ≥ 3 AEs, serious AEs, discontinuations and PN were highest with VTD treatment.
- Maintenance with single-agent bortezomib was well tolerated with limited additional toxicity as compared to induction therapy.
- Triplet therapy with VTD or VMP appears to offer little advantage over doublet therapy with VD for improving RRs and survival in elderly patients with newly diagnosed, HDT-SCT-ineligible MM.
- Because alternative VMP regimens based on less intensive bortezomib dosing have showed activity in this patient population (*JCO* 2010;28:5101), weekly dosing may be preferable in the community-based setting.

Niesvizky R et al. *Proc ASH* 2011;Abstract 478.

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Investigator Commentary: Efficacy and Safety of 3 Bortezomib Combinations in Elderly Patients with Newly Diagnosed MM: Phase IIIb UPFRONT Study Results

These results help in our understanding of the impact of weekly maintenance therapy with bortezomib. In general bortezomib is well tolerated and a viable option when offered as doublet therapy (such as VD) for elderly patients. In this randomized study VD was as effective as VTD and VMP in terms of long-term outcome. This should make clinicians comfortable with administering VD. At this point, the administration of VD subcutaneously is also a good option for elderly patients, especially for patients with underlying neuropathy, but one that must be approached with some caution. For example, I would start up-front therapy with VD by IV for a patient with aggressive newly diagnosed myeloma with high-risk features, in addition to perhaps considering a third agent, and then proceed with subcutaneous administration if PN developed. This is not only because bortezomib-induced PN is reversible and typically manageable, but also because in some patients with more advanced disease responsiveness can be lost with subcutaneous administration. This can be restored with IV therapy, suggesting that C max (which is the key difference between the 2 routes of administration) may matter in certain settings.

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