



Key ASH Presentations
Issue 7, 2012

Final Results of the Phase III VISTA Trial: VMP versus MP for Previously Untreated 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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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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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 antitumor 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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Final Results of the Phase III VISTA Trial: VMP versus MP for Previously Untreated MM

Presentation discussed in this issue

San Miguel JF et al. **Continued overall survival benefit after 5 years' follow-up with bortezomib-melphalan-prednisone (VMP) versus melphalan-prednisone (MP) in patients with previously untreated multiple myeloma, and no increased risk of second primary malignancies: Final results of the phase 3 VISTA trial.** *Proc ASH* 2011; **Abstract 476**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Sagar Lonial, MD (1/25/12)

Continued Overall Survival Benefit After 5 Years' Follow-Up with Bortezomib-Melphalan-Prednisone (VMP) versus Melphalan-Prednisone (MP) in Patients with Previously Untreated Multiple Myeloma, and No Increased Risk of Second Primary Malignancies: Final Results of the Phase 3 VISTA Trial

San Miguel JF et al.

Proc ASH 2011;Abstract 476.

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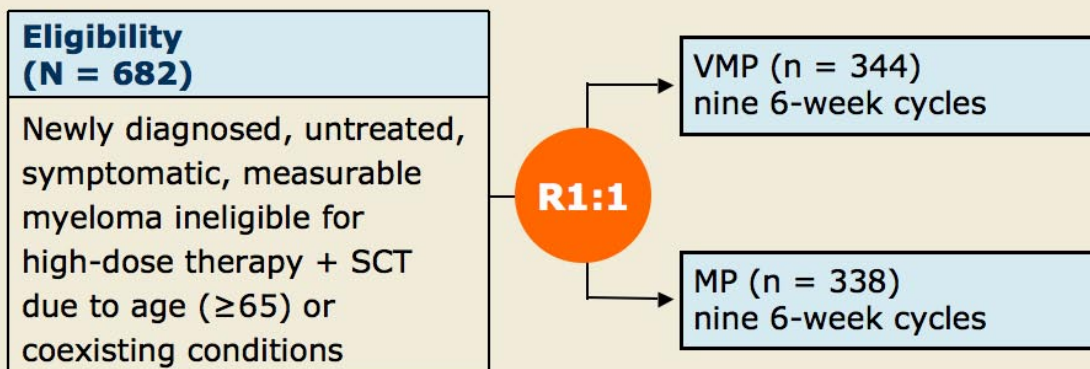
Background

- The initial report of VISTA with a median follow-up of 16.3 months demonstrated that VMP was superior to MP in response rates, time to progression and overall survival (OS) (*NEJM* 2008;359:906).
 - Demonstrations of OS improvement are difficult as a result of availability of highly effective treatments for subsequent therapy and lack of longer-term follow-up.
- Some MM therapeutic agents are associated with increased risk of second primary malignancies (SPMs).
- **Current Study Aim:**
 - Final updated OS analysis after a median follow-up of 60.1 months with analysis of impact of subsequent therapy
 - Exploratory analysis of SPMs with long-term bortezomib use in VMP vs MP

San Miguel JF et al. *Proc ASH* 2011;Abstract 476.

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VISTA Study Design



Primary endpoint: Time to disease progression

Patients are evaluated at least every 12 weeks for survival and subsequent therapy use.

Data on SPMs were collected from 655 patients (96%) by individual patient queries at all study sites during February 2011.

San Miguel JF et al. *Proc ASH* 2011;Abstract 476.

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OS Analyses

Patient group	MP	VMP	Hazard ratio	p-value
Intent-to-treat (n = 338, 344)	43.1 mo	56.4 mo	0.69	0.0004
High-risk cytogenetics* (n = 20, 26)	50.6 mo	44.1 mo	0.85	0.759
Age <75 (n = 237, 258)	47.7 mo	58.6 mo	0.68	—
Age ≥75 (n = 101, 115)	32.9 mo	50.7 mo	0.71	—
ISS Stage I (n = 64, 67)	NA	NA	0.8	—
ISS Stage II (n = 159, 176)	43.3 mo	56.4 mo	0.69	—
ISS Stage III (n=115, 130)	30.5 mo	42.1 mo	0.67	—
Creatinine Clr ≥60 mL/min (n = 154, 175)	52.7 mo	56.2 mo	0.72	—
Creatinine Clr <60 mL/min (n = 184, 198)	36.7 mo	56.8 mo	0.70	—

* Any of t(4;14), t(14;16), del(17p)

San Miguel JF et al. *Proc ASH* 2011;Abstract 476.

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OS Analyses According to Subsequent Therapies

	MP	VMP	Hazard ratio	p-value
OS from start of subsequent therapy ¹	26.8 mo	28.1 mo	NR	NR
OS of all patients receiving subsequent therapy ²	46.4 mo	55.7 mo	0.75	0.016
OS of patients who have not relapsed or received salvage bortezomib ³	45.4 mo	56.4 mo	0.71	0.0029

¹ VMP does not induce more resistant relapses.

² Bias against VMP resulting from omission of higher proportion of VMP versus MP patients who experienced the most benefit from treatment (ie, those who had not yet required subsequent therapy — 35% versus 23%).

³ Analysis includes all VMP patients versus MP patients who have not received second-line therapy (as a result of not having relapsed or because of death) and those who received salvage bortezomib.

San Miguel JF et al. *Proc ASH* 2011;Abstract 476.

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SPMs: Exposure-Adjusted Incidence Rate

SPM incidence rate, n per 100 patient-years	VMP (N = 327)	MP (N = 328)	RR
Exposure, patient-years	1,167	1,004	—
Hematologic SPMs	0.26	0.30	0.86
Fatal	0.17	0.30	0.57
Nonhematologic SPMs	1.40	1.00	1.39
Fatal	0.52	0.60	0.86
Overall rate	1.66	1.30	—
Background rate, all cancers, general US population aged 65-74 years, 2004-2008 ¹	1.92		—

- No increased risk of SPMs with addition of bortezomib to MP
- Overall incidence rates in both arms consistent with background rate of all cancers in the general US population aged 65-74 years (*SEER Cancer Statistics Review 1976-2008*).

San Miguel JF et al. *Proc ASH* 2011;Abstract 476.

Author Conclusions

- Persistent significant OS benefit was observed after a median of 60.1 months of follow-up (13.3-month improvement) with VMP vs MP.
 - Seen across multiple prespecified subgroups
 - Maintained after 5 years' follow-up and despite substantial use of novel agent-based salvage therapies
- OS subanalyses in patients receiving subsequent therapy demonstrate importance of providing optimal first-line treatment incorporating bortezomib rather than reserving bortezomib for salvage therapy and using conventional first-line treatment.
- No emerging safety signal for SPMs following VMP.
 - Thorough data collection, with <5% of patients lost to follow-up

San Miguel JF et al. *Proc ASH* 2011;Abstract 476.

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Investigator Commentary: Continued OS Benefit After 5 Years' Follow-Up with VMP versus MP in Patients with Previously Untreated Multiple Myeloma: Final Phase III VISTA Trial Results

This study provides the longest follow-up that has been performed in a large international, randomized, Phase III trial. As shown in this study, with 5 years of follow-up the VMP treatment arm continues to demonstrate improved survival in comparison to MP. This reinforces the concept that the type of treatment administered at the initial stage of the disease can affect the entire natural history in an older patient. I would argue that a similar trend will probably occur in younger patients. However, because younger patients live much longer than older patients, such a trend would be harder to see than it is in this trial. Overall, I strongly believe that choosing the right treatment regimen early on is, in fact, critically important to changing the natural history of the disease.

Interview with Sagar Lonial, MD, January 25, 2012

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