# 5 Minute JournalClub

***Key ASH Presentations***
Issue 7, 2012

# Bortezomib with Thalidomide or with Prednisone as Maintenance Therapy for Elderly Patients with MM: The GEM20005MAS65 Trial

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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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Key ASH Presentations
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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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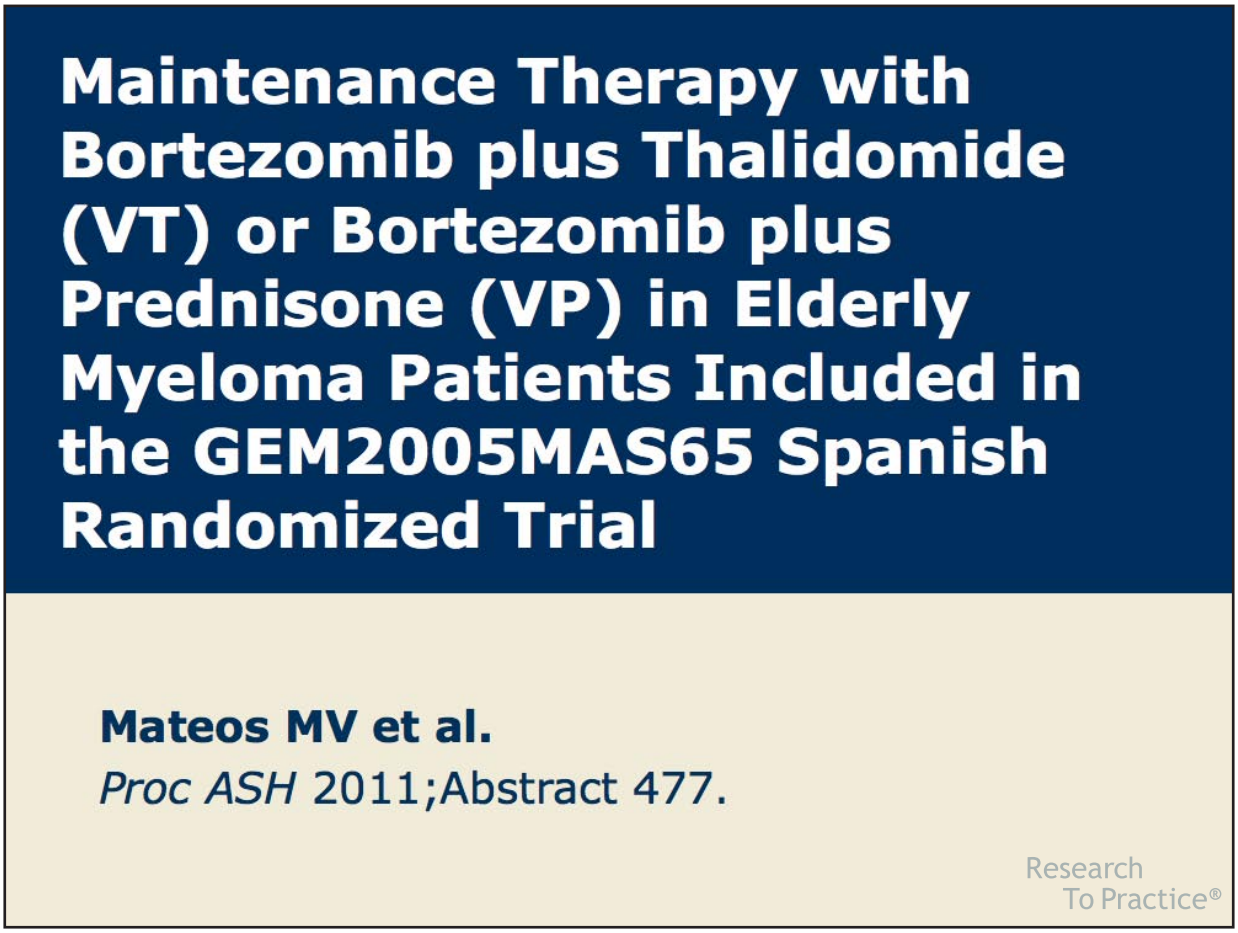
# Bortezomib with Thalidomide or with Prednisone as Maintenance Therapy for Elderly Patients with MM: The GEM20005MAS65 Trial

## Presentation discussed in this issue

Mateos MV et al. **Maintenance therapy with bortezomib plus thalidomide (VT) or bortezomib plus prednisone (VP) in elderly myeloma patients included in the GEM2005MAS65 Spanish randomized trial.** *Proc ASH* 2011;**Abstract 477**.

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



# Background

- In 2005 the Spanish Myeloma Group (GEM/PETHEMA) activated a 2-stage randomized trial in patients with untreated myeloma.
- No significant differences were observed in ORR or CR rate between patients receiving induction therapy with bortezomib/melphalan/prednisone (VMP) and those receiving bortezomib/thalidomide/prednisone (VTP) in the first stage of this trial (*Lancet Oncol* 2010;11:934).
- In the second stage, patients were randomly assigned to maintenance therapy with bortezomib in combination with prednisone (VP) or thalidomide (VT).
- **Current study objective:** Compare the efficacy and safety of maintenance therapy with VT versus VP in the second stage of the trial.

Mateos MV et al. *Proc ASH* 2011;Abstract 477.

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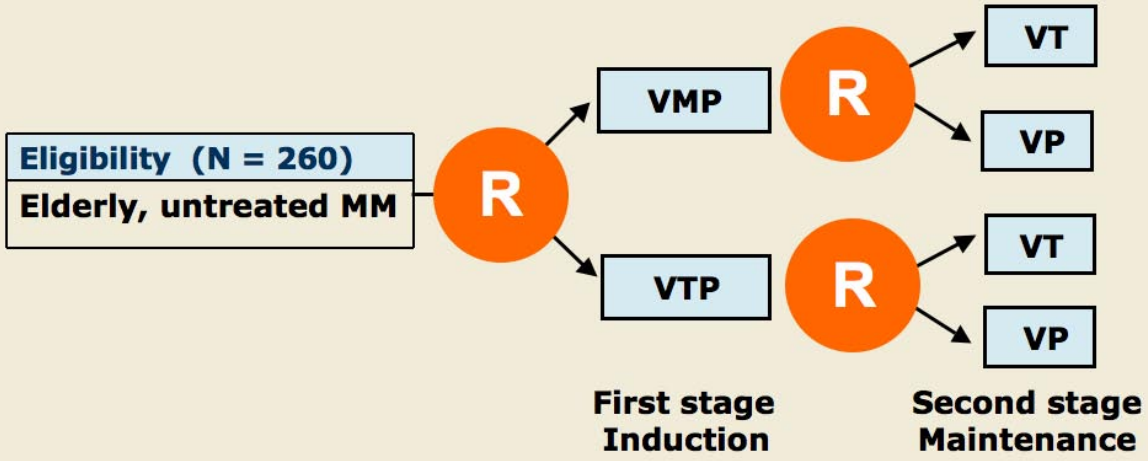
# GEM2005MAS65 Study Design




- Bortezomib was administered once a week for induction.
- Patients completing 6 induction cycles without disease progression or toxicity were moved to the second stage of maintenance.

Mateos MV et al. *Proc ASH* 2011;Abstract 477.

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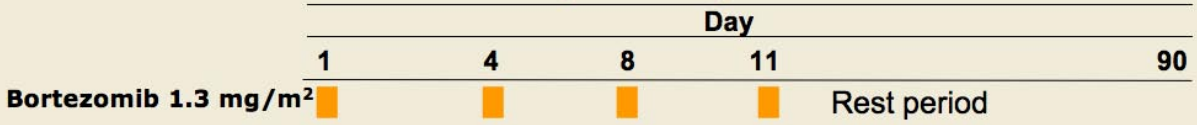
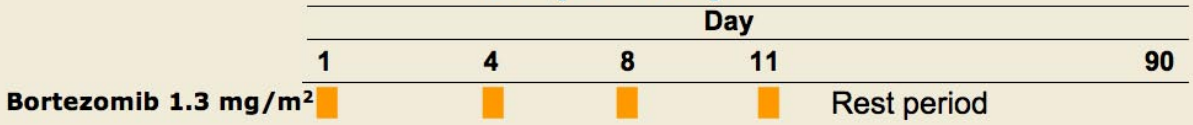
# Dosing Schedule for Maintenance Therapy

## VT (n = 91)




- **Thalidomide, 50 mg daily up to 3 years**

## VP (n = 87)




- **Prednisone, 50 mg every 48 h up to 3 years**

Bortezomib was administered every 3 months up to 3 years.

With permission from Mateos MV et al. *Proc ASH* 2011;Abstract 477.

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# Response to Maintenance Therapy

| | Premaintenance | VT (n = 91) | VP (n = 87) |
|---|---|---|---|
| **IF-CR** | 24% | 46% | 39% |
| **IF+CR** | 10% | 10% | 11% |
| **PR** | 47% | 39% | 47% |
| **MR** | 8% | 3% | 1% |
| **SD** | 10% | 1% | 1% |

IF = immunofixation; CR = complete response; PR = partial response; MR = minimal response; SD = stable disease

After a median of 20 months of maintenance therapy, no significant difference in response was observed between the VT and VP arms.

Mateos MV et al. *Proc ASH* 2011;Abstract 477.

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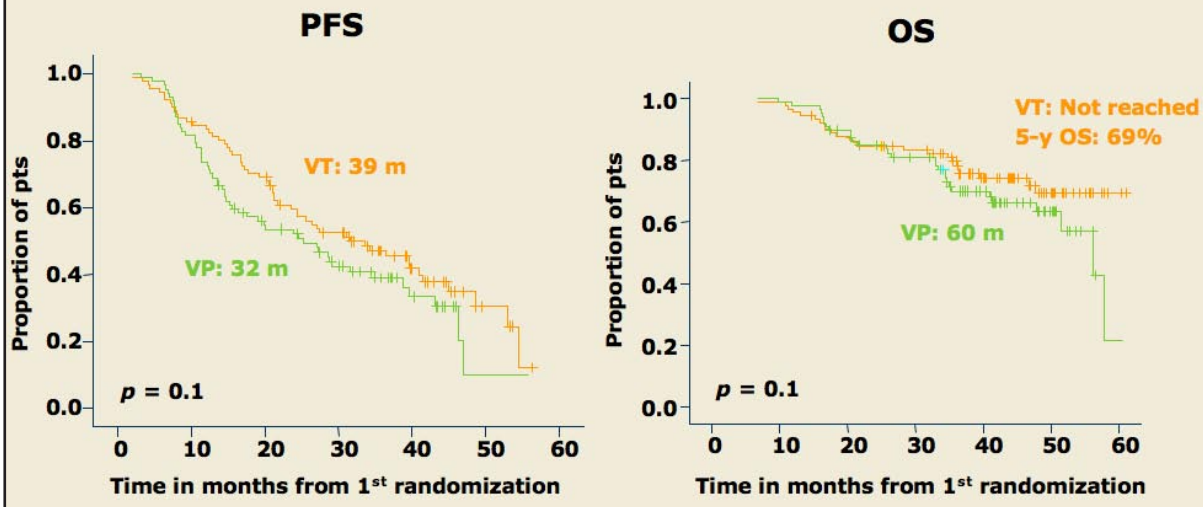
# Progression-Free Survival (PFS) and Overall Survival (OS) According to the Maintenance Arm




- Median follow-up: 46 months
- PFS and OS: n = 178

With permission from Mateos MV et al. *Proc ASH* 2011;Abstract 477.

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# Selected Adverse Events

| Adverse event | VT (n = 91) | | VP (n = 87) | |
|---|---|---|---|---|
| | Grade 1/2 | Grade 3/4 | Grade 1/2 | Grade 3/4 |
| Anemia | — | — | 1% | — |
| Thrombocytopenia | 2% | — | — | — |
| Neutropenia | 3% | 1% | — | — |
| GI symptoms | 7% | 4% | 2% | 1% |
| Peripheral neuropathy | 37% | 9% | 17% | 3% |
| Cardiac events | 5% | 2% | — | 1% |

- Second primary malignancies: VT (n = 3), VP (n = 1)
- Deaths: VT (total: 26%, disease progression: 20%, toxicity: 6%)
  VP (total: 35%, disease progression: 30%, toxicity: 5%)

Mateos MV et al. *Proc ASH* 2011;Abstract 477.

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# Author Conclusions

- Maintenance therapy with VT or VP improved the ORR and CR rate after soft induction therapy.
- No significant differences were observed between the maintenance arms, but a trend to better outcome was evident for VT.
- The toxicity profile was acceptable and slightly higher for the VT arm.
- Both maintenance regimens do not overcome the poor prognosis of high-risk cytogenetic abnormalities (data not shown).
- These bortezomib-based maintenance regimens represent an attractive platform for further optimization.

Mateos MV et al. *Proc ASH* 2011;Abstract 477.



## Investigator Commentary: Maintenance with Bortezomib in Combination with Thalidomide or Prednisone in Elderly Patients with Myeloma

This update of the Spanish GEM2005MAS65 trial provides strong supportive data for bortezomib-based therapy as maintenance because an improvement in response was reported in both arms with its use, and interestingly, there was a trend toward a better outcome for the VT group. What is also exciting is that the PFS approached 40 months, which is remarkable, although the VT arm had more toxicity.

In my view this is a nice proof-of-principle trial showing that the IMiD/proteasome inhibitor platform is effective in this setting, but care regarding side effects is important. Thus, this study opens the door to combining bortezomib with lenalidomide for maintenance therapy with less neurotoxicity and better tolerability.

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

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