5 Minute JournalClub

POST-ASH Issue 5, 2013

Overall Survival with Bortezomib (V)/Melphalan (M)/Prednisone (P)/ Thalidomide (T) and VT Maintenance versus VMP for 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

- Consider the benefits and risks of the investigational agent MLN9708 for patients with previously untreated multiple myeloma.
- Evaluate the efficacy and safety of carfilzomib with or without immunomodulatory drugs for newly diagnosed or relapsed/refractory multiple myeloma.
- Assess emerging clinical trial data on the novel combination of bendamustine, bortezomib and dexamethasone in relapsed/refractory multiple myeloma.
- Determine the maximum tolerated dose of pomalidomide in combination with bortezomib and low-dose dexamethasone for relapsed or relapsed/refractory multiple myeloma.
- Compare and contrast the effects of bortezomib/melphalan/prednisone/thalidomide followed by maintenance bortezomib/thalidomide to those of bortezomib/melphalan/prednisone on the overall survival of patients with relapsed/refractory multiple myeloma.

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Kenneth C Anderson, MD
Kraft Family Professor of Medicine
Harvard Medical School
Director, Jerome Lipper Multiple Myeloma Center
Director, LeBow Institute for Myeloma Therapeutics
Dana-Farber Cancer Institute
Boston, Massachusetts

Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Gilead Sciences Inc, Onyx Pharmaceuticals Inc, Sanofi; Other Remunerated Activities: Acetylon Pharmaceuticals Inc.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: April 2013
Expiration date: April 2014

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POST-ASH Issue 5, 2013

New proteasome inhibitor-based combination regimens in multiple myeloma

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

Dr Ken Anderson's memorable Karnofsky Award presentation at ASCO 2011 provided an intriguing overview of how profoundly the clinical face of multiple myeloma (MM) has changed in the postchemotherapy era, and the recent approval of 2 new agents is additional evidence of how quickly things are moving forward. In a previous issue of this series we focused on immunomodulatory drugs, including the recently (February 8) FDA-approved pomalidomide (Pom) for relapsed/refractory disease, and in this issue we look at the other key class of agents that has revolutionized the treatment of MM, proteasome inhibitors, which were the focus of Dr Anderson's lecture and much of his clinical and laboratory research at Dana-Farber.

In retrospect, it seems intuitive to block the mechanism by which proteins are processed and excreted in cells that are noteworthy for protein overproduction — specifically immunoglobulins — but while the translational science behind these molecules is fascinating, perhaps more important is the bottom line in terms of patient impact. In a recent ***JCO* editorial** Drs Sagar Lonial and Jonathan Kaufman make a compelling argument that in stark contrast to, for example, metastatic breast cancer, where sequential single agents are used, in MM combination regimens, although not usually curative, seem to yield better long-term outcomes. As bortezomib (BTZ) is a standard part of 2 of the most commonly used pretransplant induction regimens — RVD and CyBorD — and carfilzomib is now available for general use, it is easy to see how crucial these agents have become. Even more, at ASH we saw many interesting papers looking at various new proteasome inhibitor-based combinations that may one day soon be a part of the next generation of MM care.

1. Carfilzomib (CFZ)

This first-in-class irreversible proteasome inhibitor was approved last July for relapsed/refractory disease, but even before then there was considerable interest in testing it up front. At ASH 2011 Dr Andrzej Jakubowiak presented impressive Phase I findings with "CRd" in which the proteasome inhibitor was CFZ rather than BTZ, and this year an

NCI team added to the database by reporting **a Phase II trial of 15 patients**. Once again this combo was found to have a profound antimyeloma effect (14 responses) with acceptable tolerability and no reported Grade ≥3 peripheral neuropathy (PN).

Similarly, Dr Antonio Palumbo presented results from **a Phase II trial evaluating another CFZ combination** (CFZ/cyclophosphamide/low-dose dexamethasone [dex], or CCd) as up-front therapy in 58 patients over age 65 or ineligible for transplant. Study participants received 9 cycles of CCd followed by CFZ maintenance until progression. Of note, responses were seen in all patients, including those with adverse cytogenetics, and the progression-free survival at 1 year was 88%. Again, no Grade ≥3 PN was reported.

Finally, in the relapsed/refractory setting, **yet another CFZ triplet — CFZ/Pom/low-dose dex — showed encouraging activity**, with 15 of 30 patients responding, including many who had received extensive prior treatment and/or had adverse cytogenetics.

2. Ixazomib

Formerly MLN9708, this boron acid-based proteasome inhibitor in clinical trial development is similar to BTZ but not only seems to cause less PN but is also orally administered, opening up the enticing possibility of an all-oral RVD-like induction regimen. At ASH we saw **updated data from a Phase I/II study** of ixazomib/lenalidomide/low-dose dex in 64 patients with previously untreated MM. Importantly, 92% responded and only 2 developed Grade 3 PN (3%), helping to significantly increase enthusiasm for ongoing Phase III efforts evaluating this combination versus lenalidomide/low-dose dex in previously untreated patients.

3. More on bortezomib

Bendamustine has a similar structure to alkylating agents and is thought to perhaps have synergistic activity with BTZ. For that reason, **a Phase II study looked at a CyBorD-like** regimen in which bendamustine was substituted for cyclophosphamide. Although significant activity was observed, including responses in 48 of 71 patients (68%), it is unclear whether this regimen will be used in US practice until further data emerge.

As usual Dr Paul Richardson was quite busy at ASH, and among his oral presentations was a **Phase I study evaluating BTZ/Pom/low-dose dex** in patients with relapsed/refractory MM. While data from only 15 patients were reported, the results suggest that BTZ in combination with POM is well tolerated and highly active, further justifying the ongoing Phase III clinical trial examining this strategy.

While we are all familiar with triplet regimens, many have wondered whether 4-drug combos might provide even greater benefit, and to that end, at ASH Dr Palumbo provided **updated results from his Phase III study** of BTZ/melphalan/prednisone/thalidomide (VMPT) with VT maintenance versus VMP alone in patients who were not transplant candidates. Previous reports showed that the quartet plus maintenance provided significantly longer disease control, and in Atlanta we came to learn that it also resulted in an overall survival advantage (HR 0.7). Of interest, patients (particularly those older than 75 years of age) in the VMPT-VT arm more commonly had to discontinue therapy or reduce the BTZ dose, suggesting that less intense therapy might be preferable, but Dr Anderson believes that subcutaneous weekly BTZ may allow more patients to be treated with this approach.

Next on this series… You've heard of "R squared" (lenalidomide/rituximab). How about "R squared/CHOP"? Check out our coverage of 2 major papers on this regimen in diffuse large B-cell lymphoma and other related ASH lymphoma papers.

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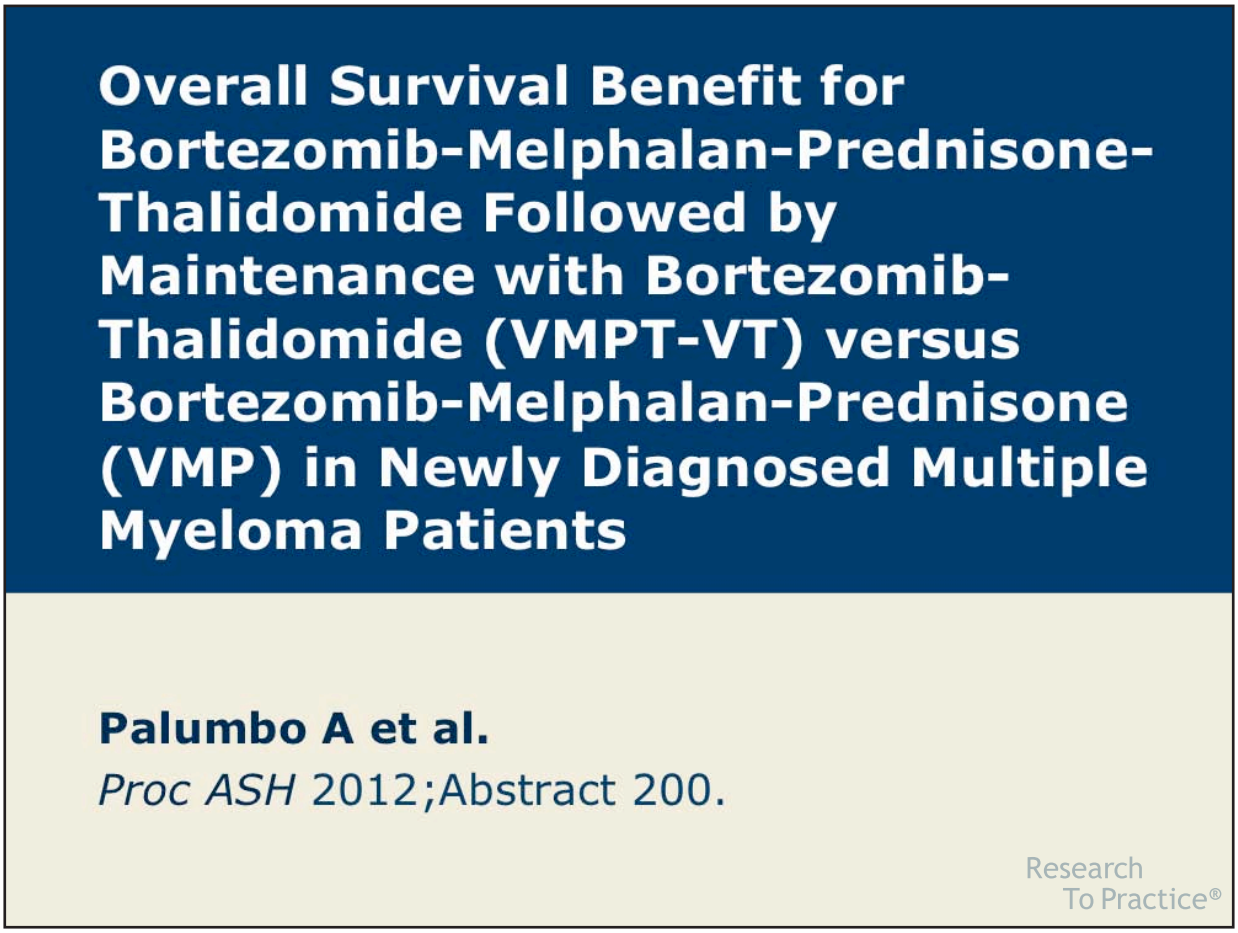
Overall Survival with Bortezomib (V)/Melphalan (M)/ Prednisone (P)/Thalidomide (T) and VT Maintenance versus VMP for Newly Diagnosed MM

Presentation discussed in this issue

Palumbo A et al. **Overall survival benefit for bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in newly diagnosed multiple myeloma patients.** *Proc ASH* 2012;**Abstract 200**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Kenneth C Anderson, MD (3/29/13)



Background

- A Phase III trial demonstrated that VMPT followed by VT (VMPT-VT) was superior to VMP alone in patients with multiple myeloma (MM) who are ineligible for autologous stem cell transplant (ASCT) (*JCO* 2010;28(34):5101).
  - 3-year progression-free survival rate:
    56% (VMPT-VT), 41% (VMP); HR = 0.67; $p = 0.008$
  - 3-year overall survival rate:
    89% (VMPT-VT), 87% (VMP); HR = 0.92; $p = 0.77$
  - Overall response rate (ORR):
    89% (VMPT-VT), 81% (VMP); $p = 0.01$
- **Study objective:** To report updated analysis of OS benefit for patients with newly diagnosed MM treated with VMPT-VT versus VMP after 4 years of follow-up.

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

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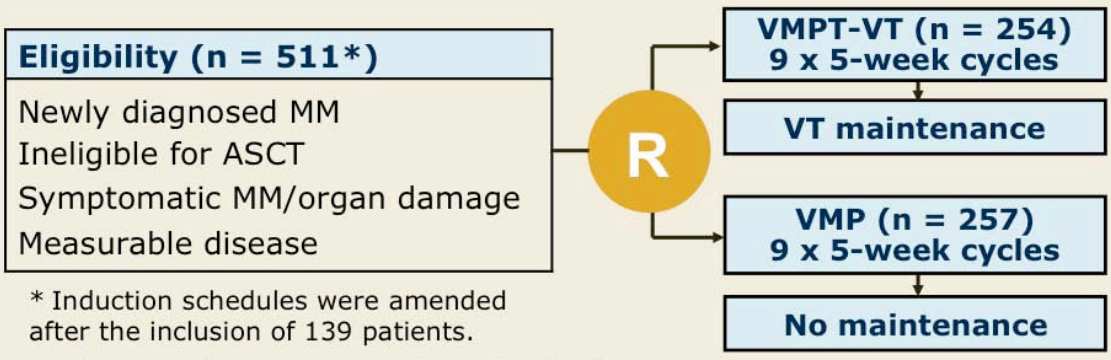
Phase III Trial Design



* Induction schedules were amended after the inclusion of 139 patients.

V: Bortezomib 1.3 mg/m^2 IV d1, 8, 15, 22
M: Melphalan 9 mg/m^2 d1-4
P: Prednisone 60 mg/m^2 d1-4
T: Thalidomide 50 mg/d continuously

- 66 (VMP) and 73 (VMPT-VT) patients received twice-weekly V
- **Primary endpoint:** Progression-free survival (PFS)
- **Secondary endpoints included:** Overall survival (OS), time to next therapy (TTNT) and safety

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

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PFS, TTNT and OS (All Patients)

Outcome	VMPT-VT	VMP	HR	*p*-value
Median PFS	35.3 mo	24.8 mo	0.58	<0.0001
Five-year PFS	29%	13%		
Median TTNT	46.6 mo	27.8 mo	0.52	<0.0001
Five-year TTNT	41%	19%		
Median OS	Not reached	60.6 mo	0.70	0.01
Five-year OS	61%	51%		

Median follow-up: 54 months

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

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One-Year Landmark Analysis*

Outcome	VMPT-VT	VMP	HR	*p*-value
Median PFS	31.5 mo	17.8 mo	Not reported	Not reported
Four-year PFS	33%	16%		
Median OS	Not reached	54.2 mo	0.63	0.006
Four-year OS	67%	55%		

* Landmark analysis was performed with patients who completed induction.

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

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Landmark Analysis* of OS by Subgroup

Subgroup	VMPT-VT vs VMP	
	HR	*p*-value
Age <75 years	0.60	0.009
Age ≥75 years	0.76	0.36
ISS 1 to 2	0.66	0.05
ISS 3	0.64	0.22
Complete response	0.45	0.01
VGPR/PR	0.80	0.28

* Landmark analysis was performed with patients who completed induction.

- ISS = International Staging System; PR = partial response; VGPR = very good PR
- HR <1.0 favors VMPT-VT

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

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OS After Relapse

	VMPT-VT	VMP	HR	*p*-value
Median OS	27.8 mo	27.3 mo	0.92	0.63
Three-year OS	47%	46%		

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

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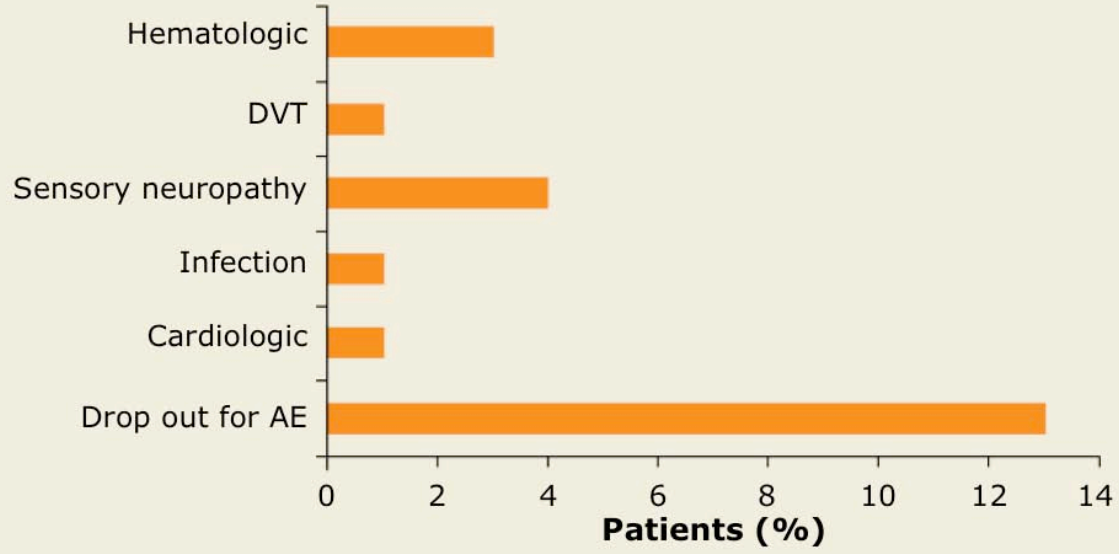
Grade 3 or 4 Adverse Events (AEs) During VT Maintenance



Newly occurring or worsening Grade 3-4 adverse events

With permission from Palumbo A et al. *Proc ASH* 2012;Abstract 200.

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Treatment Discontinuation Due to AEs

	VMPT → VT	VMP
Discontinuation rate, %		
65-75 years old	25	15
>75 years old	35	16
Bortezomib dose intensity, %		
65-75 years old	81	89
>75 years old	58	80

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

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Author Conclusions

- For patients with newly diagnosed MM who were ineligible for ASCT, treatment with VMPT-VT significantly prolonged 5-year PFS, TTNT and OS compared to VMP alone.
  - 5-year PFS: 29% vs 13%; $p < 0.0001$
  - 5-year TTNT: 41% vs 19%; $p < 0.0001$
  - 5-year OS: 61% vs 51%; $p = 0.01$
    - Prolonged OS was observed especially in patients <75 years old and in patients achieving CR after induction.
- No significant difference was observed between treatment arms in the 3-year OS rate after relapse:
  - 47% (VMPT-VT) vs 46% (VMP); $p = 0.63$

Palumbo A et al. *Proc ASH* 2012;Abstract 200.

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Investigator Commentary: Phase III Trial of VMPT-VT versus VMP Alone for Patients with Newly Diagnosed MM

In this study both PFS (35.3 vs 24.8 mo) and TTNT (46.6 vs 27.8 mo) were statistically significantly prolonged with the 4-drug and maintenance (VMPT-VT) regimen compared to VMP alone. Maintenance therapy decreased the risk of death by 30%, and OS was not reached in the VMPT-VT arm but was 60.6 months with VMP. OS from relapse was equivalent in both arms. Importantly, patients in the VMPT-VT arm more commonly had to discontinue therapy or reduce bortezomib dose, particularly patients older than 75 years.

This study demonstrated impressive 5-year PFS, TTNT and OS rates with VMPT-VT. However, the high discontinuation rate, especially among patients older than 75 years, suggests that less intensive therapies should be administered. Notably, this was the first study to show decreased neuropathy without compromising efficacy with the use of weekly bortezomib. Subcutaneous administration also reduces the neurotoxity of bortezomib. Therefore, VMPT-VT utilizing weekly and subcutaneous bortezomib may allow more patients to continue this regimen with high frequency and extent of response in addition to the prolonged PFS and OS observed in this study.

Interview with Kenneth C Anderson, MD, March 29, 2013