5 Minute JournalClub

Key ASH Presentations
Issue 1, 2011

Bortezomib-Based Maintenance Therapy for Elderly Patients with Newly Diagnosed Multiple Myeloma (MM)

For more visit ResearchToPractice.com/5MJCASH2011

Research To Practice®

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 from a plethora of ongoing clinical trials 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 and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

LEARNING OBJECTIVES

- Consider the safety and efficacy of weekly bortezomib maintenance therapy after initial up-front therapy for elderly patients with newly diagnosed MM.
- Counsel appropriately selected elderly patients with MM about the safety and efficacy of up-front bortezomib/melphalan/prednisone/thalidomide (VMPT) followed by maintenance therapy with bortezomib/thalidomide (VT).

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentation, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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:

Rafael Fonseca, MD
Consultant, Professor of Medicine
Mayo Clinic Arizona
Deputy Director, Mayo Clinic Cancer Center
Scottsdale, Arizona

Consulting Agreements: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genzyme Corporation, Medtronic Inc, Otsuka Pharmaceutical Co Ltd; Paid Research: Celgene Corporation, Onyx Pharmaceuticals Inc.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Lilly USA LLC, Millennium Pharmaceuticals Inc, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This program is supported by educational grants from Allos Therapeutics, Celgene Corporation, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc and Seattle Genetics.

Last review date: January 2011
Expiration date: January 2012

5 MinuteJournalClub

Key ASH Presentations
Issue 1, 2011

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

One can make the argument that the past few years have seen more important new agents, regimens and trial reports in multiple myeloma than any other corner of oncology, including breast cancer. At last month's ASH meeting in Orlando, we once again saw a staggering array of presentations and posters that both shed light on and add complexity to the management of this fascinating disease. In this, the first of nine brief ASH "highlight reels," we capsulize a number of key papers related to up-front treatment of multiple myeloma:

1. **The new "RVD"?**
Three years after Paul Richardson's landmark presentation of unprecedented outcomes for induction with lenalidomide, bortezomib and dexamethasone (RVD), Andrzej Jakubowiak wowed the masses in Orlando with results of a Phase I/II study of the irreversible proteasome inhibitor carfilzomib in combination with len and dex. These early efficacy data look a lot like what had been previously seen with RVD (100 percent response rate, 63 percent ≥VGPR) but with essentially no peripheral neuropathy. Stay tuned.

2. **Lenalidomide maintenance continues to impress.**
In an important trend related to the benefits of more prolonged treatment, further follow-up of the IFM trial first presented at ASCO continues to demonstrate an important advantage to maintenance len after transplant. A related paper by Antonio Palumbo — in the nontransplant setting — in which len maintenance was used after induction with melphalan/lenalidomide/prednisone also showed favorable results.

3. **Longer-term bortezomib in the up-front setting appears safe and effective in older patients.**
The UPFRONT trial showed impressive efficacy and acceptable neurotoxicity when weekly maintenance bortezomib was utilized after bortezomib-based initial induction regimens. Another paper by Palumbo also reported high response rates with bortezomib/melphalan/prednisone/thalidomide (VMPT) followed by weekly maintenance bortezomib/thalidomide (VT). As has been previously reported, neurotoxicity was reduced significantly when weekly as opposed to biweekly bortezomib was utilized.

4. **More data support low-dose dex with lenalidomide induction (Rd).**
A new analysis from the landmark ECOG trial clearly demonstrates that even in younger patients, lower-dose dex results in better outcomes.

Finally, we can happily report that the increasingly complex treatment algorithms for myeloma are being successfully implemented in daily practice. A **cross-sectional case survey of patients treated in a community setting in the last two years** reported as a poster by our CME group at the ASH meeting demonstrates consistently high response rates with modest toxicities in patients older and younger than age 75.

This Friday we will welcome eight noted clinical researchers to our recording studio in Miami for our third annual NHL/CLL Think Tank, and for the next issue of this series we'll provide you with their thoughts on ASH, including perspectives on the long-awaited findings from the Intergroup trial comparing rituximab monotherapy to "watch and wait."

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates each of the four educational activities, comprised of a slide set, for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Bortezomib-Based Maintenance Therapy for Elderly Patients with Newly Diagnosed Multiple Myeloma (MM)

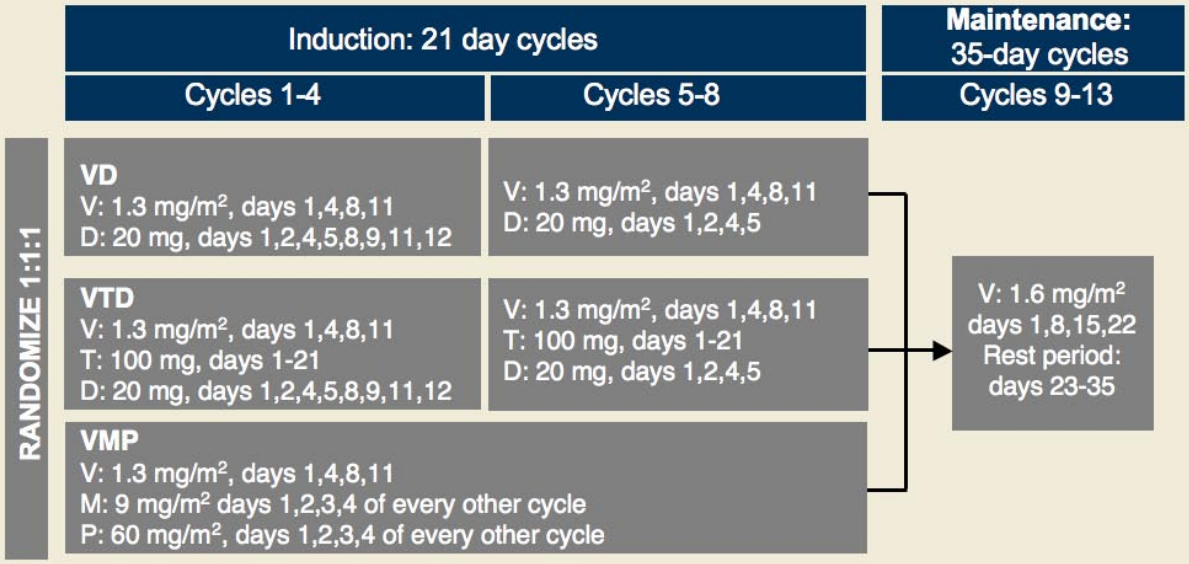
Presentations discussed in this issue

Niesvizky R et al. **Phase 3b UPFRONT study: Safety and efficacy of weekly bortezomib maintenance therapy after bortezomib-based induction regimens in elderly, newly diagnosed multiple myeloma patients.** *Proc ASH* 2010;**Abstract 619**.

Palumbo A et al. **Bortezomib, melphalan, prednisone and thalidomide followed by maintenance with bortezomib and thalidomide (VMPT-VT) for initial treatment of elderly multiple myeloma patients: Updated follow-up and impact of prognostic factors.** *Proc ASH* 2010;**Abstract 620**.

Slides from presentations at ASH 2010 and transcribed comments from a recent interview with Rafael Fonseca, MD (12/22/10)

UPFRONT Study Schema



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

Niesvizky R et al. *Proc ASH* 2010;Abstract 619.

Research To Practice®

Efficacy Endpoints

	VD (n = 167)	VTD (n = 168)	VMP (n = 167)
Median PFS	13.8 mos	18.4 mos	17.3 mos

Response rates after induction therapy (I) and after V maintenance (M)

	VD		VTD		VMP	
	I	M	I	M	I	M
ORR	68%	71%	78%	79%	71%	73%
CR + nCR	24%	31%	36%	38%	31%	34%
≥VGPR	36%	39%	44%	47%	40%	44%

CR = complete response; nCR = near CR; ORR = overall response rate; PFS = progression-free survival; VGPR = very good partial response

Niesvizky R et al. *Proc ASH* 2010;Abstract 619.

Research To Practice®

Select Grade ≥3 Adverse Events (AE)

	VD		VTD		VMP	
	I (n = 99)	M (n = 55)	I (n = 93)	M (n = 31)	I (n = 99)	M (n = 43)
Peripheral neuropathy (PN)	15%	5%	26%	6%	20%	2%
Grade ≥3 PN resulting in discontinuation of all study drugs	4%	4%	13%	0%	14%	0%
Fatigue	8%	4%	15%	0%	8%	0%
Neutropenia	1%	0%	3%	0%	21%	0%
Diarrhea	8%	5%	4%	3%	7%	7%
Pneumonia	11%	0%	6%	0%	4%	5%

Niesvizky R et al. *Proc ASH* 2010;Abstract 619.

Research To Practice®

Conclusions

- All three regimens were active in the treatment of elderly patients with newly diagnosed multiple myeloma.
  - Grade ≥3 AEs, serious AEs, PN and study discontinuations due to AEs were highest in the VTD arm.
- Single-agent bortezomib maintenance therapy post induction resulted in some increase of ≥VGPR rates in all three arms and was well tolerated.
  - Compared to post-induction rates, the rates of all-grade and Grade ≥3 PN did not increase substantially in any of the three treatment arms.
- PFS appeared similar between the treatment arms in the intent-to-treat population.

Niesvizky R et al. *Proc ASH* 2010;Abstract 619.

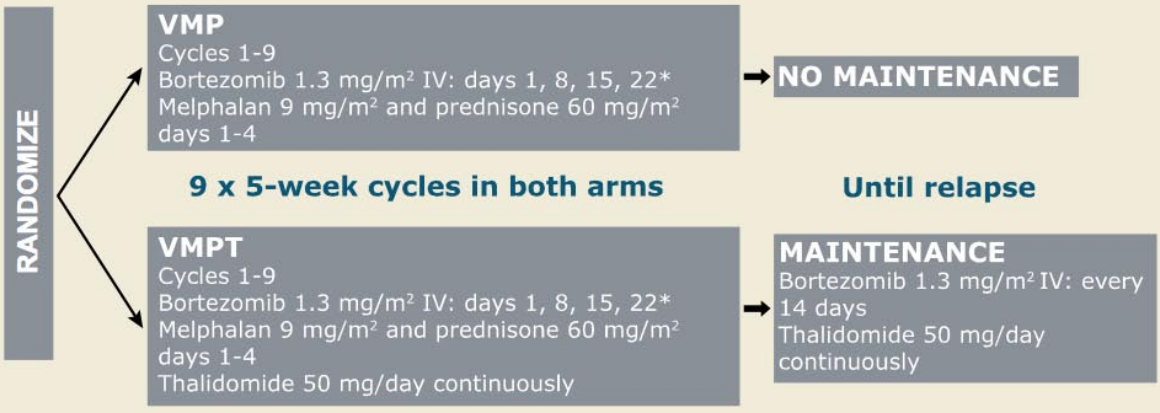
Research To Practice®

Bortezomib, Melphalan, Prednisone and Thalidomide Followed by Maintenance with Bortezomib and Thalidomide (VMPT-VT) for Initial Treatment of Elderly Multiple Myeloma Patients: Updated Follow-Up and Impact of Prognostic Factors

Palumbo A et al.

Proc ASH 2010;Abstract 620.

Study Schema

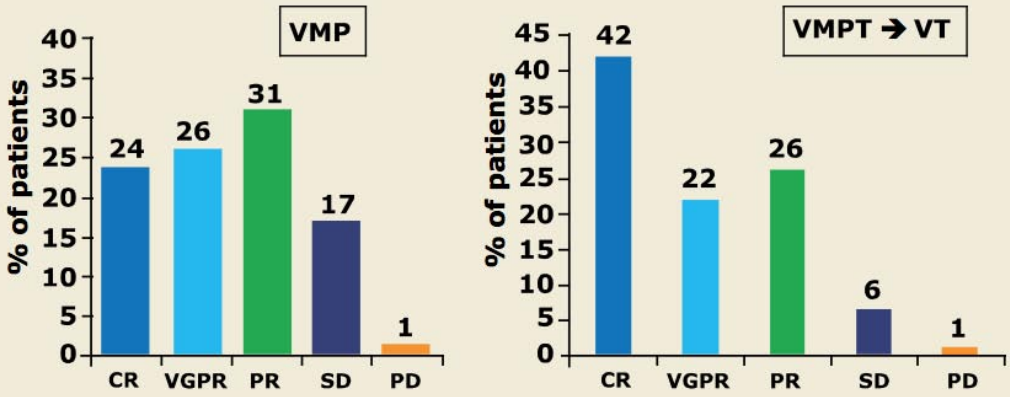


* 66 VMP patients and 73 VMPT patients were treated with twice weekly infusions of bortezomib

Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Best Response Rates

	VMP (N = 253)	VMPT-VT (N = 250)	*p*-value
CR	24%	42%	<0.0001
≥VGPR	50%	64%	0.001
≥PR	81%	90%	0.007



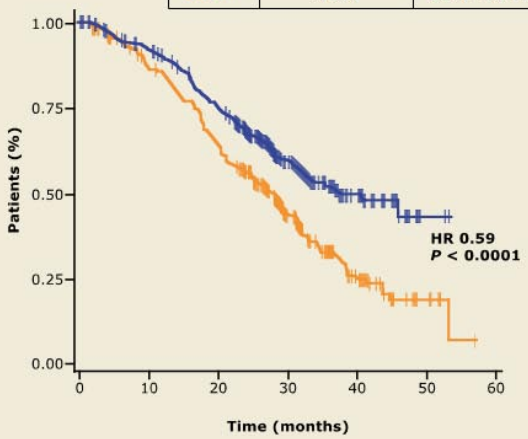
With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Research To Practice®

Results: Progression-Free Survival and Time to Next Therapy

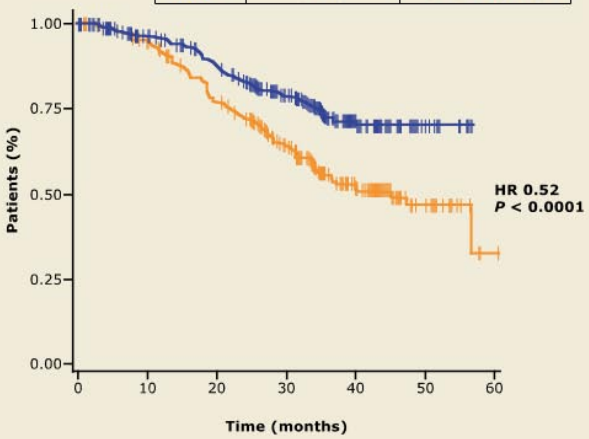
Progression-Free Survival
41% Reduced Risk of Progression

	3-years PFS	Median PFS
VMPT	51%	37.2 months
VMP	32%	27.4 months



Time to Next Therapy
48% Reduced Risk of Progression

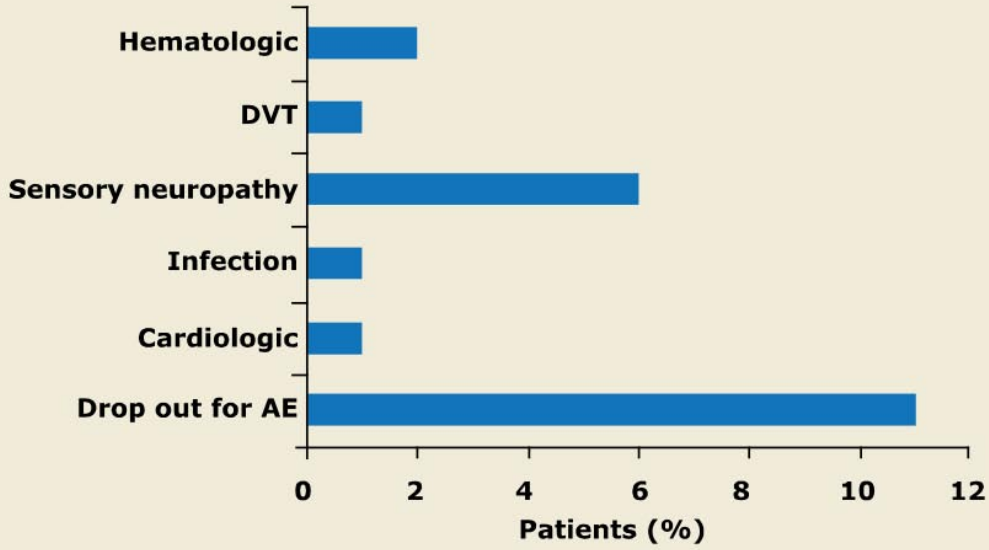
	3-years TNT	Median TTNT
VMPT	70%	Not reached
VMP	51%	37.6 months



With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Research To Practice®

Grade 3 or 4 Adverse Events After Cycle 9 (Maintenance Phase)

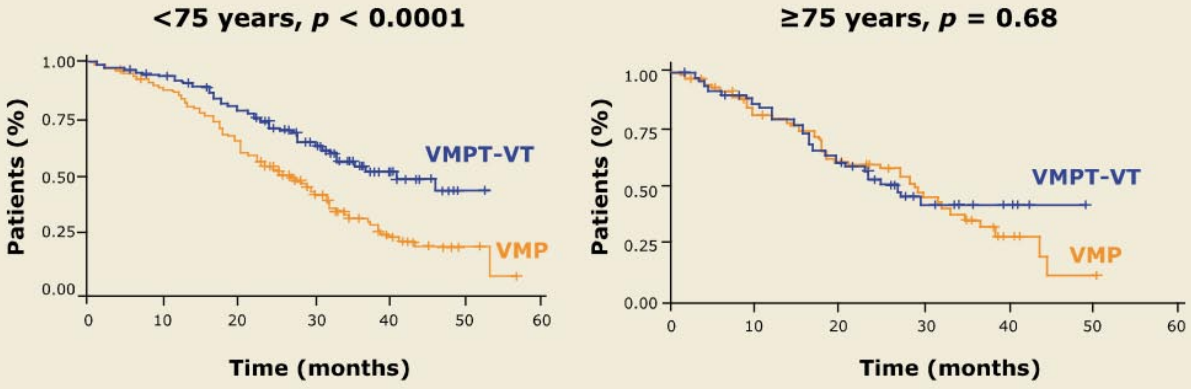


Newly occurring or worsening Grade 3 or 4 adverse events

With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Research To Practice®

PFS According to Age



With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Research To Practice®

Conclusions

- Statistically significant improvements reported with VMPT → VT versus VMP for treatment of newly diagnosed MM.
  - CR rate: 42% vs 24% ($p < 0.0001$)
  - Median PFS: 37 months vs 27 months ($p < 0.0001$)
- VMPT → VT prolonged PFS with an unprecedented 3-year PFS of 55% in elderly patients (data not shown).
- Higher dose-intensity regimens seemed to be less effective in frail patients (≥75 years).
- Maintenance therapy with VT further improved PFS with a good safety profile.

Palumbo A et al. *Proc ASH* 2010;Abstract 620.

Investigator comment on bortezomib-based maintenance regimens as part of initial management of myeloma in elderly patients

The UPFRONT study presented by Dr Niesvizky is important because it addressed the role of maintenance therapy for patients who normally would otherwise receive a short duration of treatment. The main point of this paper is that a longer duration of therapy with bortezomib maintenance, after initial induction, improves the response rates and the duration of disease control. For certain patients, such as those with high-risk disease, bortezomib maintenance is not only appropriate but also desirable.

The study presented by Dr Palumbo showed a high degree of activity with VMPT. The postinduction maintenance approach included the combination of two of the most active class of agents: proteasome inhibitors and IMiDs®. In my opinion VMPT is probably not ready for prime time as similar efficacy outcomes from three-drug combinations could also be seen. The maintenance part of the study confirms that the duration of therapy is important in the management of myeloma.

Interview with Rafael Fonseca, MD, December 22, 2010