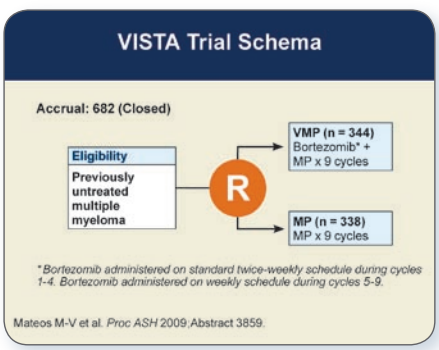
# Year in Review

## Multiple Myeloma: 2009-2010

**A CME monograph and speaker's slide kit summarizing the year's most important meeting presentations and journal articles**





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EDITOR

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**Monograph**

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Year in Review — Multiple Myeloma: 2009-2010

# *Year in Review* — Multiple Myeloma: 2009-2010
# Continuing Medical Education (CME) Information

## OVERVIEW OF ACTIVITY

Multiple myeloma (MM) accounts for approximately 10 percent of all hematologic cancer cases and carries with it the worst death to new cases ratio (3:4) of all the subtypes. The American Cancer Society has estimated 20,580 new MM cases in the United States in 2009, with an estimated 10,580 deaths. The treatment of MM has improved dramatically during the past decade, particularly with the advent of novel agents, and the budding landscape surrounding the optimal treatment of MM is both exciting and complex. Knowledge of the many therapeutic advances and changing practice standards is essential to ensuring optimal patient outcomes. To bridge the gap between research and patient care, this CME activity utilizes the input of cancer experts and community physicians to frame a relevant discussion of recent research advances in myeloma that can be applied to routine clinical practice. This information will help medical oncologists, hematologists and hematology-oncology fellows formulate up-to-date clinical management strategies.

## LEARNING OBJECTIVES

- Effectively apply the results of pivotal clinical research to the clinical management of newly diagnosed and relapsed MM.
- 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.
- Use biomarkers to assess risk for patients with MM, and recommend systemic treatment commensurate with prognosis and likelihood of therapeutic response.
- Recognize treatment-associated side effects, and offer patients prophylactic or acute supportive management strategies to address them.
- Differentiate emerging investigational compounds from existing agents used in the treatment of MM.
- Identify current approaches to stem cell transplant for eligible patients with symptomatic MM, and recommend evidence-based induction regimens to facilitate long-term outcomes.
- Recall the design and eligibility criteria for ongoing clinical trials in newly diagnosed and relapsed MM, and enroll or refer appropriate patients for study participation.

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## COMMERCIAL SUPPORT

This program is supported by an educational grant from Millennium Pharmaceuticals Inc.

## PHARMACEUTICAL AGENTS DISCUSSED IN THIS PROGRAM

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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: **Dr Giralt** — **Advisory Committee and Speakers Bureau:** Celgene Corporation, Eisai Inc, Genzyme Corporation, Millennium Pharmaceuticals Inc; **Consulting Agreements:** Genzyme Corporation, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation; **Paid Research:** Novartis Pharmaceuticals Corporation. **Dr Jagannath** — **Advisory Committee:** Merck and Company Inc, Millennium Pharmaceuticals Inc. **Dr Orlowski** — **Sponsored Research Agreements:** Celgene Corporation, Centocor Ortho Biotech Services LLC, Millennium Pharmaceuticals Inc. **Dr Richardson** — **Advisory Committee:** Celgene Corporation, Millennium Pharmaceuticals Inc.

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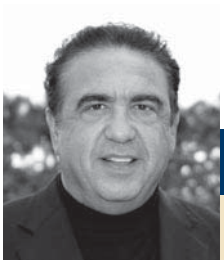


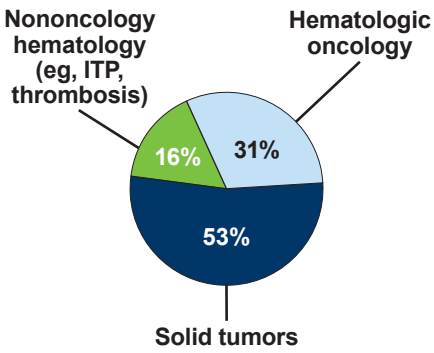
NEIL LOVE, MD

## An important disease

As part of a recent national survey our CME group conducted with 100 US-based medical oncologists, participants were asked to estimate the fraction of patients in their practices with various hematologic cancers. As in our other surveys of this type, clinicians reported that approximately one third of their patients were diagnosed with these diverse diseases (Figure 1).

1

**February 2010 Survey of 100 US-Based Medical Oncologists: Approximately what percentage of your practice involves the following areas?**




While representing a "minority" of oncology practice, the huge volume of important clinical research information that is emerging in each one of these complex blood and/or lymphoid neoplasias is equal to, if not greater than, the amount of new data in several much more common solid tumors. In response, our group has in recent years introduced a number of time-saving tools to help clinicians access information and perspectives on hematologic cancers. Our *Hematologic Oncology Update* audio program is a good example in that it allows users to multitask and learn about AML, NHL, MM, et cetera as they drive, work out and participate in a number of other pretty interesting activities, including gardening, mowing the lawn and simmering in the hot tub.

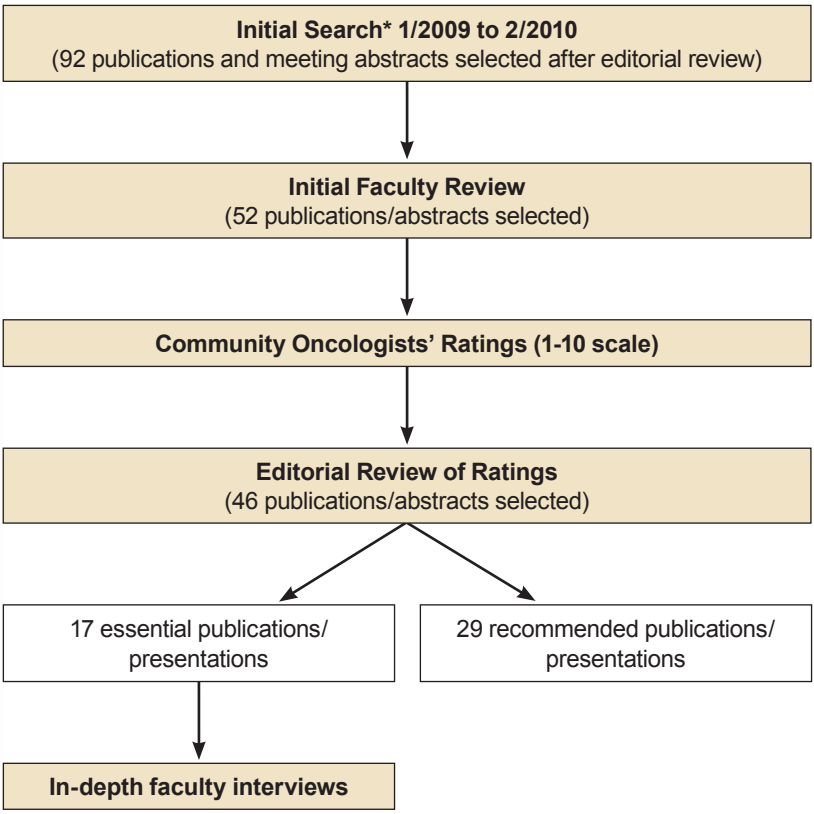
Our *Year in Review* series is another attempt to bring efficiency into education. For each one of these adventures, we use the RTP "home-brewed" peer-review process involving clinical investigators and practicing oncologists, working with us to identify key new data sets relevant to research and practice (Figure 2). The enclosed *YiR* focuses on what our aforementioned survey documents to be one of the most common hematologic cancers seen in practice — multiple myeloma (Figure 3). This second myeloma issue of the series is again designed to provide access to the most up-to-date and important research data available in this not-so-uncommon disease, as we provide graphical summaries — and a PowerPoint version available for downloading at ResearchToPractice.com — of 17 "tier one" papers or presentations considered essential for clinicians and an annotated bibliography of 29 "tier two" publications considered important but less critical to know about (see pages 5 and 49).

For all of the important studies profiled here, ideally oncologists should attempt to read the actual papers and watch the virtual presentations if available. (Come on ASH!) As a supplement or perhaps a replacement, we hope you will find this presentation useful, beneficial and time saving.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
May 3, 2010

**2**

## Process for Identifying Key Recent Reports on the Management of Multiple Myeloma




*** PubMed. January 1, 2009 to February 9, 2010, English language, clinical trials, randomized clinical trials, practice guidelines, meta-analysis, classical article, clinical trial (Phase II, III, IV), comparative study, controlled clinical trial, multi-center study, validation studies. Search of meeting abstracts from 2009 ASH and ASCO annual meetings.**

**3**

## February 2010 Survey of 100 US-Based Medical Oncologists: How many total and new patients have you seen in the past year?

| | Total patients Median | New patients Median |
|---|---|---|
| NHL | 35 | 10 |
| CLL | 30 | 5 |
| MM | 30 | 15 |
| MDS | 25 | 6 |
| ITP | 15 | 5 |
| CML | 10 | 3 |
| AML | 5 | 3 |
| APL | 1 | 1 |
| Adult ALL | 1 | 1 |

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## PRIORITY 1 PUBLICATIONS/PRESENTATIONS (ESSENTIAL)

### UP-FRONT/INDUCTION THERAPY

Palumbo A et al. **A Phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma.** *Proc ASH* 2009;Abstract 613.

Mateos M-V et al. **A prospective, multicenter, randomized, trial of bortezomib/melphalan/prednisone (VMP) versus bortezomib/thalidomide/prednisone (VTP) as induction therapy followed by maintenance treatment with bortezomib/thalidomide (VT) versus bortezomib/prednisone (VP) in elderly untreated patients with multiple myeloma older than 65 years.** *Proc ASH* 2009;Abstract 3.

Cavo M et al. **A Phase III study of double autotransplantation incorporating bortezomib-thalidomide-dexamethasone (VTD) or thalidomide-dexamethasone (TD) for multiple myeloma: Superior clinical outcomes with VTD compared to TD.** *Proc ASH* 2009;Abstract 351.

Rajkumar SV et al; for the Eastern Cooperative Oncology Group. **Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: An open-label randomised controlled trial.** *Lancet Oncol* 2010;11(1):29-37.

Gay F et al. **Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: A comparative analysis of 411 patients.** *Blood* 2010;115(7):1343-50.

Harousseau J-L et al. **High complete and very good partial response rates with bortezomib–dexamethasone as induction prior to ASCT in newly diagnosed patients with high-risk myeloma: Results of the IFM2005-01 Phase 3 trial.** *Proc ASH* 2009;Abstract 353.

Mateos M-V et al. **Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: Updated follow-up and impact of subsequent therapy in the Phase III VISTA trial.** *J Clin Oncol* 2010;[Epub ahead of print].

### RELAPSED/REFRACTORY DISEASE

Richardson PG et al. **Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: Impact of a dose-modification guideline.** *Br J Haematol* 2009;144(6):895-903.

Reece D et al. **Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: Adverse effect of deletion 17p13.** *Blood* 2009;114(3):522-5.

Richardson P et al. **Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma.** *Blood* 2009;114(4):772-8.

### TREATMENT GUIDELINES/CONSENSUS PAPERS

National Comprehensive Cancer Network. **NCCN clinical practice guidelines in oncology: Multiple myeloma.** v.3.2010. Available at: www.nccn.org.

Palumbo A et al, on behalf of the IMWG. **International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation.** *Leukemia* 2009;23(10):1716-30.

Fonseca R et al, on behalf of the International Myeloma Working Group. **International Myeloma Working Group molecular classification of multiple myeloma: Spotlight review.** *Leukemia* 2009;23(12):2210-21.

Dispenzieri A et al, on behalf of the International Myeloma Working Group. **International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders.** *Leukemia* 2009;23(2):215-24.

Terpos E et al; European Myeloma Network. **The use of bisphosphonates in multiple myeloma: Recommendations of an expert panel on behalf of the European Myeloma Network.** *Ann Oncol* 2009;20(8):1303-17.

### INVESTIGATIONAL AGENTS

Lacy MQ et al. **Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma.** *J Clin Oncol* 2009;27(30):5008-14.

Siegel D et al. **PX-171-004, an ongoing open-label, Phase II study of single-agent carfilzomib (CFZ) in patients with relapsed or refractory myeloma (MM); Updated results from the bortezomib-treated cohort.** *Proc ASH* 2009;Abstract 303.

# A Phase III Study to Determine the Efficacy and Safety of Lenalidomide in Combination with Melphalan and Prednisone Followed by Lenalidomide (MPR-R) in Patients ≥ 65 Years with Newly Diagnosed Multiple Myeloma (NDMM)

**Palumbo A et al.**

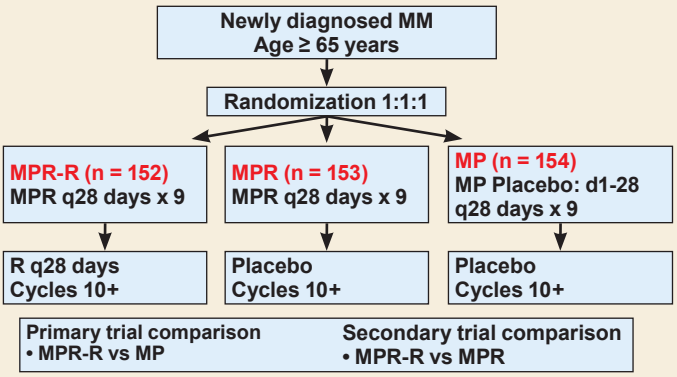
*Proc ASH* 2009;Abstract 613.

## Introduction

- **Prolonged lenalidomide therapy has been shown to improve overall survival in patients with relapsed/refractory multiple myeloma (ASH 2008;Abstract 3702).**
- **Phase I/II study has demonstrated that MPR is an effective therapy with manageable toxicity for patients with NDMM (*Clin Lymphoma Myeloma* 2009;9:145).**
- **Current study objective:**
  - **Compare the efficacy and safety of MPR with or without lenalidomide maintenance with that of MP alone in patients with NDMM.**

Palumbo A et al. *Proc ASH* 2009;Abstract 613.

## Phase III, Multicenter, Randomized Trial of MPR in Elderly Patients with NDMM




Palumbo A et al. *Proc ASH* 2009;Abstract 613.

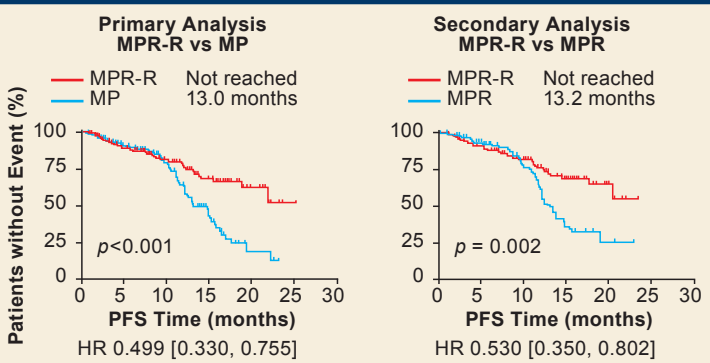
## Clinical Response

| Best overall response* | MPR-R (n = 152) | MPR (n = 153) | MP (n = 154) | *p*-value MPR-R vs MP |
|---|---|---|---|---|
| Overall response rate | 77% | 67% | 48% | <0.001 |
| Complete response | 18% | 13% | 5% | <0.001 |
| ≥Very good partial response | 32% | 33% | 11% | <0.001 |
| Partial response | 45% | 34% | 37% | — |
| Progressive disease | 0% | 1% | 0% | — |
| Median time to first response | 1.9 mo | 1.9 mo | 2.8 mo | <0.001 |

**Measured by EBMT criteria*

Palumbo A et al. *Proc ASH* 2009;Abstract 613.

## Median Progression-Free Survival (PFS)




With permission from Palumbo A et al. *Proc ASH* 2009;Abstract 613.

## Conclusions

- **Continuous lenalidomide is superior to regimens of limited duration in patients ≥65 years with NDMM.**
- **MPR-R resulted in an approximately 50% reduced risk of progression compared to MP.**
- **MPR-R had a tolerable safety profile (data not shown).**
  - **— No Grade 3/4 peripheral neuropathy**
  - **— Grade 4 neutropenia: 36%**
- **MPR-R is a potential new standard treatment option for elderly patients with NDMM.**

Palumbo A et al. *Proc ASH* 2009;Abstract 613.

# Up-Front/Induction Therapy

## FACULTY COMMENTS

**DR RICHARDSON:** This Phase III study demonstrated the efficacy and safety of lenalidomide both as part of induction therapy in combination with MP and as maintenance therapy.

Melphalan/prednisone/lenalidomide (MPR) followed by lenalidomide causes superior responses and a substantially reduced risk of disease progression over time in comparison to MP alone.

The safety profile is manageable, with only a few patients developing neuropathy of any kind and an overall low discontinuation rate of 16 percent, even with a 36 percent rate of Grade IV neutropenia.

**DR JAGANNATH:** Even though higher numbers of responses occur with MPR without R maintenance therapy compared to MP, the progression-free survival curves are absolutely superimposable.

However, PFS is significantly superior when MPR is followed by R maintenance compared to MP. Clearly lenalidomide maintenance after melphalan/prednisone seems to be the key.

## A Prospective, Multicenter, Randomized Trial of Bortezomib/Melphalan/Prednisone (VMP) versus Bortezomib/Thalidomide/Prednisone (VTP) as Induction Therapy Followed by Maintenance Treatment with VT versus VP in Elderly Untreated Patients with Multiple Myeloma Older than 65 Years

**Mateos MV et al.**

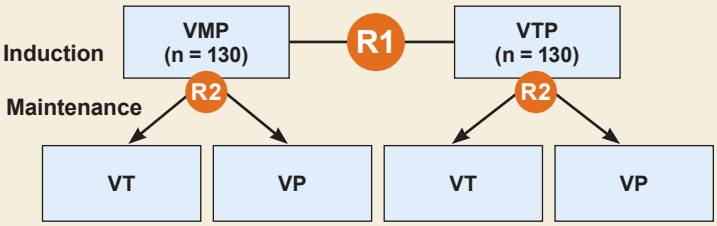
*Proc ASH* 2009;Abstract 3.

## Introduction

- **VMP is tolerable and effective in elderly patients.**
  - **— 89% ≥ PR; 32% CR (*Blood* 2006;108:2165)**
  - **— Median PFS = 25 months (*Haematologica* 2008;93:560)**
  - **— Overall survival = 50 months**
  - **— 17% GIII-IV peripheral neuropathy**
- **<u>Current study objectives</u>:**
  - **— Compare the efficacy (ORR and CR rate) of VMP vs VTP when used as induction therapy**
  - **— Assess if maintenance therapy (VT vs VP) can improve response rates with a favorable toxicity profile**
    - **– Increase CR by 15% (from 20-35% to 35-40%)**

Mateos MV et al. *Proc ASH* 2009;Abstract 3.

## Induction with VMP versus VTP Followed by Maintenance with VT versus VP for Untreated MM in Patients > 65 Years




*Bortezomib (V): Induction phase, 1.3 mg/m² twice weekly during a 6-week first cycle, then weekly during subsequent cycles; maintenance phase, 1.3 mg/m² twice weekly days 1, 4, 8 and 11 every 3 months*

Mateos MV et al. *Proc ASH* 2009;Abstract 3.

## Induction: Response and Toxicity Profile

| Response Rate (EBMT criteria) | VMP | VTP |
|---|---|---|
| ORR<br>CR immunofixation (CRIF)-negative<br>CRIF-positive | 80%<br>20%<br>12% | 81%<br>27%<br>10% |
| PR | 48% | 46% |
| **Select Adverse Events (≥G3-4)** | **VMP** | **VTP** |
| Infections | 7% | <1% |
| Peripheral neuropathy | 5% | 9% |
| Cardiologic events | 0% | 8% |

Mateos MV et al. *Proc ASH* 2009;Abstract 3.

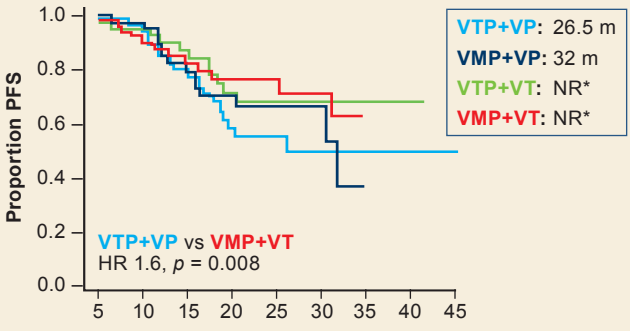
## Maintenance: Response and Toxicity Profile

| Response Rate (EBMT criteria) | VT (n = 91) | VP (n = 87) |
|---|---|---|
| CR/nCR<br>CRIF-negative<br>CRIF-positive | 59%<br>44%<br>15% | 55%<br>39%<br>16% |
| PR | 39% | 44% |
| **Select Adverse Events (≥G3-4)** | **VT (n = 91)** | **VP (n = 87)** |
| Peripheral neuropathy | 5% | 2% |
| Cardiologic events | 2% | 1% |

Mateos MV et al. *Proc ASH* 2009;Abstract 3.

# Up-Front/Induction Therapy

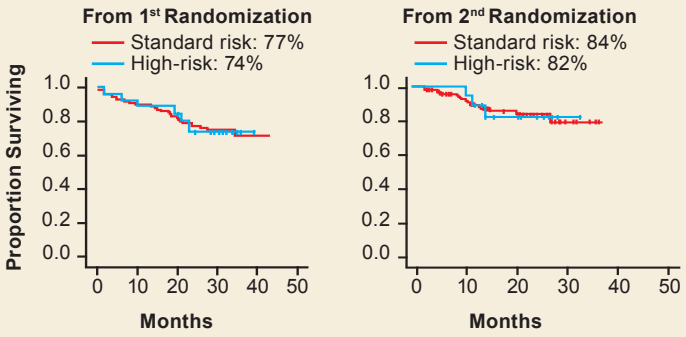
## Median PFS by Induction-Maintenance Treatment Cohorts (n = 178)




*NR = not reached*

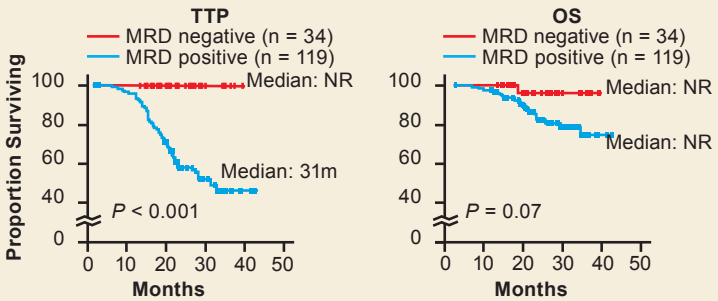
With permission from Mateos MV et al. *Proc ASH* 2009;Abstract 3.

## Two-Year Overall Survival According to Cytogenetic Risk Profile (VMP or VTP Followed by VT or VP)




With permission from Mateos MV et al. *Proc ASH* 2009;Abstract 3.

## Survival According to MRD* After Induction Therapy (VMP or VTP Followed by VT or VP)




*Minimal residual disease (MRD) assessed by immunophenotyping in bone marrow*

With permission from Mateos MV et al. *Proc ASH* 2009;Abstract 3.

## Conclusions

- **Weekly bortezomib dosing resulted in less peripheral neuropathy compared to rates seen with historical biweekly administration.**
- **Maintenance therapy increased the CR rate with an acceptable toxicity profile.**
- **Progression-free survival with induction VMP followed by maintenance VT is significantly superior to VPT-TP.**
- **The bortezomib-based combinations appeared to overcome the poor prognosis of high-risk cytogenetics.**
- **Alkylating agents remain effective drugs for elderly patients with previously untreated multiple myeloma.**

Mateos MV et al. *Proc ASH* 2009;Abstract 3.

### *FACULTY COMMENTS*

**DR RICHARDSON:** Response rates are impressive and similar with either of the three-drug induction regimens. VMP causes more myelosuppression and bortezomib/thalidomide/prednisone (VTP) is associated with cardiac events and slightly more neuropathy.

A critical aspect of this study is maintenance therapy with VT or VP. VT has a marginally worse adverse event profile, but PFS results strongly favor VT maintenance.

**DR ORLOWSKI:** Bortezomib was administered weekly after the first cycle in the induction phase, and this led to less neuropathy in both arms despite maintaining efficacy. A significant improvement in PFS occurs with VT relative to VP maintenance.

There is also a suggestion that patients who started out with VMP and then received VT maintenance therapy had the best PFS. PFS was also better for patients with no minimal residual disease (MRD) in follow-up, and this is the first time that the correlation between no MRD and positive long-term outcome has been described in myeloma.

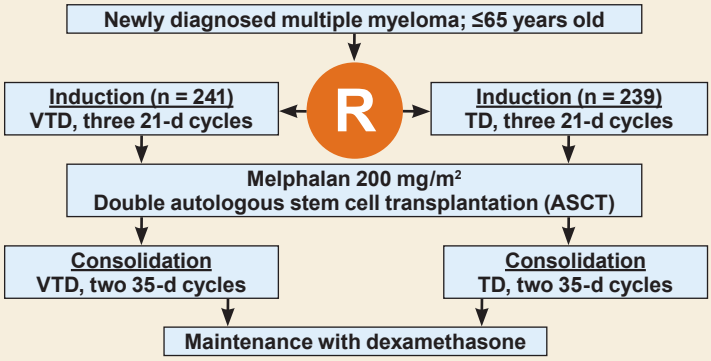
## A Phase III Study of Double Autotransplantation Incorporating Bortezomib-Thalidomide-Dexamethasone (VTD) or Thalidomide-Dexamethasone (TD) for Multiple Myeloma: Superior Clinical Outcomes with VTD Compared to TD

**Cavo M et al.**

*Proc ASH* 2009;Abstract 351.

# Up-Front/Induction Therapy

## Trial Schema




Cavo M et al. *Proc ASH* 2009;Abstract 351.

## Response to Induction Therapy Intent-to-Treat Analysis*

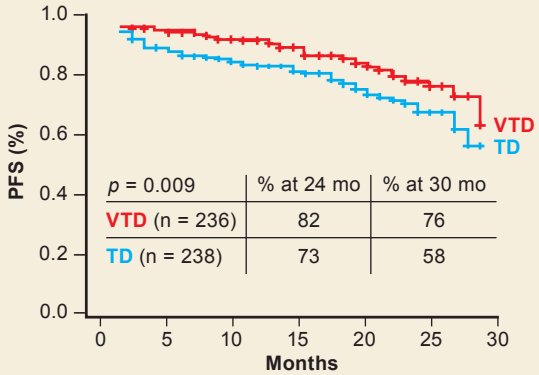
| | VTD (n = 241) | TD (n = 239) | *p*-value |
|---|---|---|---|
| CR | 57% | 31% | 0.0001 |
| CR + nCR | 70% | 51% | <0.0001 |
| ≥VGPR | 88% | 72% | <0.0001 |
| ≥PR | 95% | 89% | 0.01 |

*CR, complete response; nCR, near complete response; VGPR, very good partial response; PR, partial response*

**Responses were centrally reassessed and defined by EBMT criteria.*

Cavo M et al. *Proc ASH* 2009;Abstract 351.

## Progression-Free Survival (PFS)




With permission from Cavo M et al. *Proc ASH* 2009;Abstract 351.

## PFS in Patients with High-Risk Cytogenetic Profiles*

| | VTD | | TD | |
|---|---|---|---|---|
| | Positive | Negative | Positive | Negative |
| Events | 22.7% | 12.1% | 36% | 20.3% |
| PFS at 24 mo | 73% | 83% | 53% | 77% |
| PFS at 30 mo | 60% | 67% | 42% | 59% |
| *p*-value | 0.16 | | 0.02 | |

**Patients with t(4;14) ± del(17p)*

Cavo M et al. *Proc ASH* 2009;Abstract 351.

## Conclusions

- **VTD plus double ASCT provided superior short- and long-term outcomes to TD plus double ASCT.**
  - **— The rates of CR + nCR/≥VGPR were significantly improved with VTD vs TD.**
  - **— PFS was significantly improved with VTD vs TD.**
- **The toxicity of VTD as an induction and consolidation therapy was relatively low (data not shown).**
- **The VTD regimen may be considered as a new standard treatment option for younger ASCT-eligible patients with multiple myeloma.**

Cavo M et al. *Proc ASH* 2009;Abstract 351.

### *FACULTY COMMENTS*

**DR GIRALT:** This study shows that induction therapy before transplant makes a difference. Bortezomib/thalidomide/dexamethasone (VTD) improved complete response (CR) rates and PFS. For patients who undergo stem cell transplants, a bortezomib-containing induction therapy should be considered a standard approach.

To date, no study has compared a bortezomib-based induction therapy to a lenalidomide-based induction therapy, so both strategies could be considered appropriate for these patients.

**DR ORLOWSKI:** Notice that the induction on the VTD arm consists of three 21-day cycles — about nine weeks of induction therapy — which is substantially shorter than the standard 16 weeks of induction. Despite this limited duration, all efficacy outcomes, including CR and PFS, improved with VTD.

Incorporation of bortezomib also improved outcomes for patients at high risk. Other approaches are likely still needed to further enhance efficacy in the presence of high-risk cytogenetic features, but this is definitely an encouraging improvement in that category also.

# Lenalidomide Plus High-Dose Dexamethasone versus Lenalidomide Plus Low-Dose Dexamethasone as Initial Therapy for Newly Diagnosed Multiple Myeloma: An Open-Label Randomised Controlled Trial

**Rajkumar SV et al.**

*Lancet Oncol* 2010;11(1):29-37.

## Introduction

- **In newly diagnosed multiple myeloma (MM), the response rate with lenalidomide (R) plus high-dose dexamethasone (D) is 91% (*Blood* 2005;106:4050).**
- **Current study objective:**
  - **— Assess if R plus low-dose dexamethasone (Rd) can preserve the efficacy of RD but with reduced toxicity**
  - **— Primary study endpoint: Overall response rate (ORR) in first 4 cycles of treatment**
  - **— Survival analysis of patients who received transplant after 4 cycles vs patients who continued Rd beyond 4 cycles**

Rajkumar SV et al. *Lancet Oncol* 2010;11:29-37.

## Open-Label Trial of RD versus Rd in MM

**Accrual: 445**

**Eligibility**

**Measurable, untreated symptomatic MM or bone marrow plasmacytosis or plasmacytoma**

**Hgb > 70g/L, platelet ≥ 75x10$^9$/L, neutrophil > 1x10$^9$/L**

**R**

**R 25 mg/d + D 40 mg/d d1-4, 9-12, 17-20 q 28 days* (n = 223) x 4 cycles**

**R 25 mg/d + d 40 mg/d d1, 8, 15, 22 q 28 days* (n = 222) x 4 cycles**

**After 4 cycles, patients may proceed to stem cell transplant (SCT); patients with progression or no response may receive thalidomide + dexamethasone.*

Rajkumar SV et al. *Lancet Oncol* 2010;11:29-37.

## Select Adverse Events (AE) in First Four Months

| AE | RD (n = 223) | Rd (n = 220) | *p*-value |
|---|---|---|---|
| ≥Grade 3 | 52% | 35% | 0.0001 |
| Deaths | 5% | 0.4% | 0.003 |
| Deep vein thrombosis or pulmonary embolism | 26% | 12% | 0.0003 |
| Infection or pneumonia | 16% | 9% | 0.04 |
| Fatigue | 15% | 9% | 0.08 |

Rajkumar SV et al. *Lancet Oncol* 2010;11:29-37.

## Primary Study Results: Overall Response and Survival

| | RD (n = 214) | Rd (n = 208) | *p*-value |
|---|---|---|---|
| ORR (complete plus partial) at 4 cycles | 79% | 68% | 0.008 |
| 1-year overall survival (OS)*<br>< 65 years old<br>≥ 65 years old<br>2-year OS* | 87%<br>91%<br>83%<br>75% | 96%<br>98%<br>94%<br>87% | 0.0002 |
| Successful stem cell mobilization (n = 167) | 163 (98%) | | |

** Not a protocol-specified endpoint; study stopped at 12.5 months follow-up because of higher OS with Rd. Patients on RD crossed over to Rd.*

Rajkumar SV et al. *Lancet Oncol* 2010;11:29-37.

## Survival Outcome with Post-Induction SCT, No SCT or Continued Primary Therapy*

| Three-year overall survival | RD | Rd | *p*-value |
|---|---|---|---|
| No SCT after 4 cycles of primary therapy (n = 54, 39) | 55% | 55% | 0.631 |
| SCT after 4 cycles of primary therapy (n = 50, 40) | 92% | 92% | 0.528 |
| Primary therapy beyond 4 cycles (n = 108, 140) | 79% | 79% | Not reported |

** At four months, 183 of 431 patients alive discontinued from study +/- subsequent SCT and 248 continued primary therapy in the absence of SCT.*

Rajkumar SV et al. *Lancet Oncol* 2010;11:29-37.

# Up-Front/Induction Therapy

## Conclusions

- **Primary analysis of induction RD vs Rd**
  - **— ORR RD vs Rd: 79% vs 69% (absolute difference within prespecified margin of noninferiority)**
  - **— Lower toxicity and treatment-related mortality with Rd (0.5% vs 5.0%)**
  - **— Greater 2-year OS with Rd (87% vs 75%)**
- **Impact of SCT and continued primary therapy on outcome**
  - **— Lenalidomide plus dexamethasone may be a good option for pretransplant induction therapy (3-year OS: 92%)**
  - **— Continued primary therapy (>4 cycles) with Rd seems effective and tolerable as a front-line regimen for myeloma, particularly in the elderly**

Rajkumar SV et al. *Lancet Oncol* 2010;11:29-37.

### *FACULTY COMMENTS*

**DR GIRALT:** Survival was significantly better on the lenalidomide/low-dose dexamethasone (Rd) arm despite a lower response rate.

Rd is an excellent option for transplant-eligible patients as the three-year survival rate with Rd followed by transplant is approximately 92 percent.

This is also a good induction regimen for transplant-ineligible patients as it is well tolerated and resulted in a three-year survival rate of 55 percent for patients who did not undergo transplant.

**DR JAGANNATH:** The difference in the two arms is the intensity of dexamethasone. Lenalidomide/high-dose dexamethasone (RD) caused significant side effects, especially thrombosis and infections, and thus caused increased mortality, especially among older patients.

However, I believe RD should still be used, especially during the first cycle, for some patients — such as those with renal impairment or hypercalcemia, who need a rapid tumor response. Appropriate prophylaxis for infection and deep vein thrombosis should be administered.

## Lenalidomide Plus Dexamethasone Versus Thalidomide Plus Dexamethasone in Newly Diagnosed Multiple Myeloma: A Comparative Analysis of 411 Patients

**Gay F et al.**

*Blood* 2010;115(7):1343-50.

## Introduction

- **Lenalidomide and thalidomide are each active in combination with dexamethasone for the treatment of multiple myeloma (MM).**
  - **— Lenalidomide is more potent in preclinical assays than thalidomide, but causes more hematologic side effects (*Blood* 2002;100:3063; *NEJM* 2007;357:2123).**
- **No randomized trial of thalidomide/dexamethasone (Thal/Dex) versus lenalidomide/dexamethasone (Len/Dex) has been reported or is ongoing/planned.**
- **Current study objective:**
  - **— Compare the efficacy and toxicity of Len/Dex or Thal/Dex as initial therapy for MM using a retrospective analysis.**

Gay F et al. *Blood* 2010;115(7):1343-50.

## Methods

- **Case-control retrospective study conducted using data from 411 consecutive patients from the Mayo Clinic with newly diagnosed MM.**
  - **— Patients treated with Thal/Dex: 183 (110 received SCT)**
  - **— Patients treated with Len/Dex: 228 (111 received SCT)**
- **All patients were administered either:**
  - **— High-dose dexamethasone (40 mg orally, twice weekly)**
  - **— Low-dose dexamethasone (40 mg orally, weekly)**
- **Risk stratification of patients:**
  - **— High risk: del 17p, t(4;14), t(14;16) by FISH or loss of chromosome 13 by metaphase cytogenetics**
  - **— Standard risk: Patients without any of the above**

Gay F et al. *Blood* 2010;115(7):1343-50.

## Efficacy Outcomes

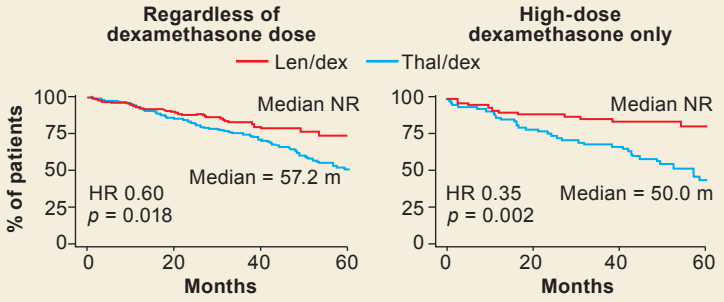
| Efficacy | Thal/Dex (n = 183) | Len/Dex (n = 228) | *p*-value |
|---|---|---|---|
| CR | 3.3% | 13.6% | <0.001 |
| ≥VGPR | 12.0% | 34.2% | <0.001 |
| ≥PR | 61.2% | 80.3% | <0.001 |
| Median time to progression | 17.2 mo | 27.4 mo | 0.019 |
| Progression-free survival | 17.1 mo | 26.7 mo | 0.036 |

*CR = complete response; VGPR = very good partial response; PR = partial response*

Gay F et al. *Blood* 2010;115(7):1343-50.

# Up-Front/Induction Therapy

## Median Overall Survival with Len/Dex versus Thal/Dex




*NR = not reached*

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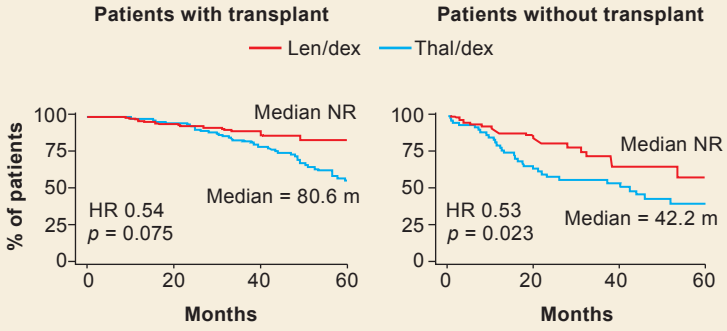
## Overall Survival with Respect To Transplantation Status

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## Grade 3 and 4 Adverse Events

| Adverse event | Thal/Dex (n = 183) | Len/Dex (n = 228) | *p*-value |
|---|---|---|---|
| Anemia | 0% | 4.4% | 0.003 |
| Thrombocytopenia | 0% | 4.8% | 0.002 |
| Neutropenia | 0.6% | 14.0% | <0.001 |
| Peripheral neuropathy | 10.4% | 0.9% | <0.001 |
| Constipation | 4.9% | 0% | 0.001 |
| Diarrhea | 0% | 3.5% | 0.01 |
| Venous thromboembolism | 15.3% | 9.2% | 0.058 |
| Infections | 8.2% | 13.1% | 0.109 |

Gay F et al. *Blood* 2010;115(7):1343-50.

## Summary


- **Len/Dex appears superior to Thal/Dex in all efficacy outcomes including overall survival.**
- **Outcomes remain superior with Len/Dex after adjusting for the dose of dexamethasone and for transplantation status.**
- **Differences in the adverse events with the two regimens are consistent with what has been previously reported.**
  - **— Hematological side effects were more common with lenalidomide; peripheral neuropathy was more common with thalidomide.**
- **Randomized trials are required for confirmation of these results.**

Gay F et al. *Blood* 2010;115(7):1343-50.


### *FACULTY COMMENTS*

**DR GIRALT:** The results of this retrospective analysis support the hypothesis that induction therapy with lenalidomide/dexamethasone (len/dex) is superior to that of thalidomide/dexamethasone (thal/dex).

The higher complete and overall response rates recorded with len/dex were statistically significant and clinically relevant.

A survival benefit was observed with len/dex as induction versus thal/dex irrespective of transplant status or whether high- or low-dose dexamethasone was administered.

In the absence of randomized clinical trials and recognizing the caveats of a retrospective study, I cannot say definitively that patients should receive induction therapy with len/dex over thal/dex.

However, in my practice I have begun to offer this as a potential induction therapy for those patients with low-risk disease, those considered to be transplant ineligible or those with preexisting neuropathy.

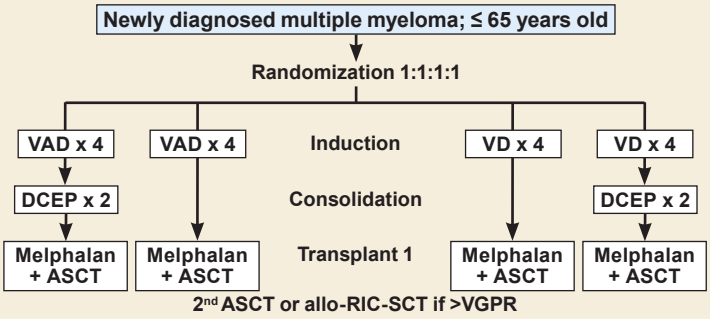
## High Complete and Very Good Partial Response Rates with Bortezomib-Dexamethasone as Induction Prior to ASCT in Newly Diagnosed Patients with High-Risk Myeloma: Results of the IFM2005-01 Phase 3 Trial

**Harousseau J-L et al.**

*Proc ASH* 2009;Abstract 353.

# Up-Front/Induction Therapy

## Trial Schema




*VAD = vincristine/doxorubicin/dexamethasone*
*VD = bortezomib/dexamethasone*

Harousseau J-L et al. *Proc ASH* 2009;Abstract 353.

## Clinical Response (≥VGPR)

| | VAD (n = 218) | VD (n = 223) | *p*-value |
|---|---|---|---|
| After induction | 16% | 39% | <0.0001 |
| After ASCT 1 | 37% | 54% | 0.0003 |
| After ASCT 2 | 47% | 68% | <0.0001 |

*A higher response rate was achieved in patients on the VD arm receiving induction therapy despite:*
- *A slightly higher proportion of patients with poor-risk cytogenetics*
- *A smaller proportion of patients having received a second ASCT*

Harousseau J-L et al. *Proc ASH* 2009;Abstract 353.

## Progression-Free Survival (PFS) Median Follow-Up 32 Months

| Patient Group | VAD | VD | *p*-value |
|---|---|---|---|
| All patients (n = 242, 240) | 30 mo | 36 mo | 0.057 |
| Patients with ISS Stage II-III (n = 136, 133) | 23 mo | 33 mo | 0.006 |
| Patients with poor cytogenetics* (n = 29, 40) | 24 mo | 33.5 mo | 0.113 |

**Patients with poor cytogenetics were defined as having t(4;14) and/or del(17p).*

Harousseau J-L et al. *Proc ASH* 2009;Abstract 353.

## Impact of Post-Induction VGPR or Better on PFS

| Patient Group | ≥VGPR | <VGPR | *p*-value |
|---|---|---|---|
| All patients (n = 117, 324) | 41 mo | 30 mo | <0.0001 |
| Patients with ISS stage II-III (n = 65, 204) | Not reached | 23 mo | <0.0001 |
| Patients with poor cytogenetics* (n = 21, 48) | 37 mo | 24 mo | 0.0036 |

**Patients with poor cytogenetics were defined as having t(4;14) ± del(17p).*

Harousseau J-L et al. *Proc ASH* 2009;Abstract 353.

## Conclusions

- **Pre-ASCT induction therapy with VD versus VAD resulted in:**
  - **— Longer PFS, irrespective of cytogenetic risk profile**
  - **— Higher rates of complete response and VGPR**
- **Achieving at least VGPR after induction therapy appears to be a major prognostic factor for improved PFS, especially in patients with high-risk multiple myeloma.**

Harousseau J-L et al. *Proc ASH* 2009;Abstract 353.

### *FACULTY COMMENTS*

**DR RICHARDSON:** The high rate of responses with bortezomib/dexamethasone (VD) versus vincristine/doxorubicin/dexamethasone (VAD) prior to transplant translated into a longer progression-free survival (PFS), suggesting that the quality of response with induction therapy before transplant really matters. This applied to patients with early-stage and advanced-stage disease in addition to those with adverse cytogenetic features.

Interestingly, achieving at least a very good partial response after induction is an important prognostic factor, especially for patients with ISS Stage II/III disease or those with adverse cytogenetic features.

**DR ORLOWSKI:** An important observation is that improvement in PFS occurred with VD in comparison to VAD despite a shorter duration of induction and the fact that a lesser proportion of patients in the bortezomib group received a second transplant.

Additionally, VD overcame the negative outcome predicted by ISS staging and poor-risk cytogenetic features like t(4;14) and/or del 17p.

# Bortezomib Plus Melphalan and Prednisone Compared with Melphalan and Prednisone in Previously Untreated Multiple Myeloma: Updated Follow-Up and Impact of Subsequent Therapy in the Phase III VISTA Trial

**Mateos M-V et al.**

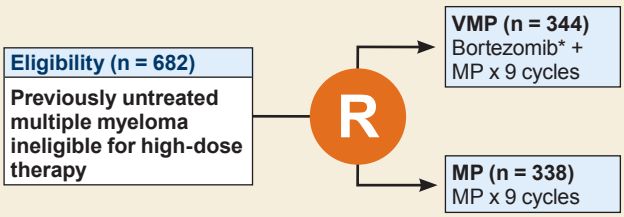
*J Clin Oncol* 2010;28(13):2259-66.

## Introduction

- **Overall survival has been shown to be improved with VMP compared with MP in previously untreated patients with multiple myeloma (MM) ineligible for transplant (*NEJM* 2008;359:906).**
- **Rescue therapies may affect overall survival in longer follow-up.**
- **Current study objective:**
  - **Examine updated survival analysis of bortezomib (V) with melphalan/prednisone (MP) versus MP alone in patients with untreated MM ineligible for high-dose therapy**

Mateos M-V et al. *J Clin Oncol* 2010;28(13):2259-66.

## VISTA Trial Schema




**Bortezomib administered on standard twice-weekly schedule during cycles 1-4. Bortezomib administered on weekly schedule during cycles 5-9.*

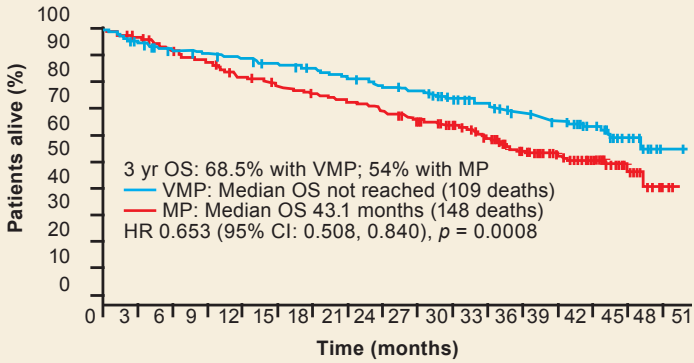
Mateos M-V et al. *J Clin Oncol* 2010;28(13):2259-66.

## Subsequent Therapy

- **52% of patients on VMP and 69% on MP have received subsequent therapy.**
- **Among patients who received subsequent therapy, 24% on VMP arm and 50% on MP arm received bortezomib.**
- **Median time to next treatment (TTNT) and treatment free interval (TFI) were significantly longer with VMP.**
  - **— 43% and 18% of VMP and MP patients, respectively, had TFI ≥ 2 years**

Mateos M-V et al. *J Clin Oncol* 2010;28(13):2259-66.

## Updated Survival Benefit with VMP (Median Follow-Up 36.7 Months)

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## Subset Analyses

- **Among those patients who received subsequent therapy, the survival benefit with VMP over MP was retained.**
- **A trend of improved survival from start of subsequent therapy was observed (HR 0.815, $p = 0.21$) in all patients who received subsequent therapy.**
- **In the VMP subgroup, OS was better among patients aged < 75 vs ≥ 75 years (HR 1.664, $p = 0.011$).**
- **No statistically significant difference in overall survival among patients treated with VMP was apparent when results were analyzed by baseline renal function or cytogenetic risk profile.**

Mateos M-V et al. *J Clin Oncol* 2010;28(13):2259-66.

## Conclusions

- **Updated analysis confirms that VMP results in significantly improved survival compared to MP.**
- **Survival benefit is seen both overall and also in patients who had received subsequent therapy.**
- **VMP results in significantly longer TTNT and TFI.**
- **Salvage therapies are similarly effective following VMP and MP, suggesting that bortezomib use as initial therapy does not induce more resistant relapse.**

Mateos M-V et al. *J Clin Oncol* 2010;28(13):2259-66.

### *FACULTY COMMENTS*

**DR RICHARDSON:** This updated analysis after more than three years of follow-up confirms that bortezomib/melphalan/prednisone (VMP) improves overall survival compared to MP, and the survival benefit is also evident among patients who received subsequent therapy. This emphasizes the fact that initial treatment matters.

The other important conclusion is that salvage therapies are similarly effective after VMP or MP and that front-line bortezomib does not induce a more resistant relapse.

**DR ORLOWSKI:** The median overall survival for patients who received MP is 43.1 months and has not yet been reached for those who received VMP. Three-year overall survival is 54 percent with MP and 68.5 percent for VMP.

Additionally, VMP improves the treatment-free interval and extends the time to next treatment.

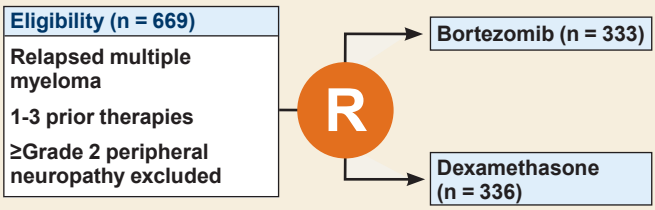
Also, the addition of bortezomib appears to be partially overcoming the adverse outcomes from high-risk cytogenetics and renal impairment.

## Reversibility of Symptomatic Peripheral Neuropathy with Bortezomib in the Phase III APEX Trial in Relapsed Multiple Myeloma: Impact of a Dose-Modification Guideline

**Richardson PG et al.**

*Br J Haematol* 2009;144(6):895-903.

## APEX Trial Comparing Bortezomib with Dexamethasone




*Bortezomib 1.3 mg/m² on d1, 4, 8 and 11 for eight 21-d cycles, and then on d1, 8, 15 and 22 for three 35-d maintenance cycles*

Richardson PG et al. *Br J Haematol* 2009;144(6):895-903; Richardson PG et al. *N Engl J Med* 2005;353(24):2487-98.

## Dose-Modification Guideline in APEX Trial for Bortezomib-Associated Neuropathy

- **Grade 1 without pain**
  - **— No action**
- **Grade 1 with pain or Grade 2**
  - **— Reduce bortezomib dosage to 1.0 mg/m²**
- **Grade 2 with pain or Grade 3**
  - **— Withhold bortezomib until toxicity resolves, then reinitiate at a dose of 0.7 mg/m² once weekly**
- **Grade 4**
  - **— Discontinue bortezomib**

Richardson PG et al. *Br J Haematol* 2009;144(6):895-903.

## Neuropathy in APEX Trial

| | All patients with ≥G 2 neuropathy (n = 91) | ≥G 2 neuropathy; dose modification (n = 72) | ≥G 2 neuropathy; no dose modification (n = 19) |
|---|---|---|---|
| Improvement/resolution of neuropathy | 58 (64%) | 49 (68%) | 9 (47%) |
| No improvement/ resolution of neuropathy | 33 (36%) | 23 (32%) | 10 (53%) |

*Mostly sensory neuropathy (98%) observed; incidence and severity was independent of age, prior thalidomide or vincristine therapy, and diabetes history.*

Richardson PG et al. *Br J Haematol* 2009;144(6):895-903.

## Dose-Modification Guidelines and Reversibility of Neuropathy

- **91/331 (27%) patients developed ≥G2 neuropathy.**
  - **— 72/91 had dose modifications per guidelines.**
  - **— 19/91 had no dose modifications (protocol violations).**
- **49/72 (68%) patients who had dose modifications experienced improvement or resolution of their neuropathy.**
- **9/19 (47%) patients who did not have dose modifications experienced resolution of their neuropathy.**

Richardson PG et al. *Br J Haematol* 2009;144(6):895-903.

## Effect of Dose Modification for Neuropathy on Outcome

| Evaluable patients | RR (CR + PR) | CR | Median TTP (mo) | Median OS (mo) |
|---|---|---|---|---|
| All (N = 315) | 43% | 9% | 6.2 | 29.7 |
| No neuropathy (n = 196) | 38% | 6% | 5.6 | 23.2 |
| G ≥ 2 neuropathy (n = 86) | 50% | 14% | 6.3 | Not estimable |
| Dose modified (n = 68) | 59% | 16% | 6.9 | Not estimable |
| No dose modification (n = 18) | 17% | 6% | 2.9 | 14.9 |

Richardson PG et al. *Br J Haematol* 2009;144(6):895-903.

## Summary and Conclusions

- **Bortezomib-associated neuropathy is predominantly sensory and is reversible in the majority of patients.**
- **Bortezomib-associated neuropathy is unaffected by age, prior therapies with neurotoxic agents or history of diabetes and thus may be mechanistically distinct.**
- **Bortezomib dose modification may ameliorate bortezomib-associated neuropathy.**
- **Bortezomib dose modification for peripheral neuropathy does not appear to adversely affect efficacy or outcome.**

Richardson PG et al. *Br J Haematol* 2009;144(6):895-903.

## *FACULTY COMMENTS*

**DR RICHARDSON:** We showed that bortezomib-associated neuropathy is largely reversible with the use of a dose-modification guideline.

Another important part of the analysis is that dose modification did not adversely affect outcome. In addition, the neuropathy was unaffected by age, prior therapies with neurotoxic agents or history of diabetes, so bortezomib-associated neuropathy could be mechanistically distinct from other etiologies.

**DR JAGANNATH:** It is important to note the bortezomib is reasonably well tolerated. While 27 percent of patients may develop ≥ Grade II neuropathy, only 9 percent had Grade III events.

In addition, compliance with dose-modification guidelines leads to a greater reversibility of neuropathy without adversely affecting the outcome.

# Influence of Cytogenetics in Patients with Relapsed or Refractory Multiple Myeloma Treated with Lenalidomide Plus Dexamethasone: Adverse Effect of Deletion 17p13

**Reece D et al.**

*Blood* 2009;114(3):522-5.

## Introduction

- **Poor prognosis exists for patients with multiple myeloma (MM) carrying t(4;14) or del(17p13) (*Blood* 2007;109:3489).**
- **Negative prognostic impact of t(4;14) is overcome with bortezomib (*N Engl J Med* 2008;359:906).**
- **Limited data exist on the role of lenalidomide in patients with "high-risk" cytogenetic abnormalities.**
- **<u>Current study objective</u>:**
  - **— Determine effects of del(13q), t(4;14) and del(17p13) in patients treated with lenalidomide (R) and dexamethasone (D) for relapsed or refractory MM.**

Reece D et al. *Blood* 2009;114(3):522-5.

## Methods

- **Post hoc subanalysis was performed on 130 patients from three Canadian centers in the Expanded Access Program database (MM-016 study), with available FISH studies for del(13q), t(4;14) and del(17p13).**
  - **— Median follow-up at 19.7 months**
  - **— Primary outcome: Time to progression (TTP)**
  - **— Secondary outcome: Overall survival (OS)**
- **Matched pair analysis was performed for the subgroup of patients with t(4;14) to address the inherent imbalance in clinical characteristics and short period of follow-up.**

Reece D et al. *Blood* 2009;114(3):522-5.

## Effect of Cytogenetics on Treatment Efficacy

| | All patients (n = 130) | del(13q) (n = 54) | del(17p13) (n = 12) | t(4;14) (n = 28) |
|---|---|---|---|---|
| Response (>minimal) | 83.1% | 77.8% ($p$ = 0.007) | 58.3% ($p$ < 0.001) | 78.5% ($p$ = 0.06) |
| Median TTP (mo) | 7.1 | 5.9 (HR = 1.42; $p$ = 0.09) | 2.22 (HR = 2.82; $p$ < 0.001) | 8.0 (HR = 1.44; $p$ = 0.137) |
| Median OS (mo) | 22.7 | 14.7 (HR = 1.43; $p$ = 0.152) | 4.67 (HR = 3.23; $p$ < 0.001) | 23.7 (HR = 1.04; $p$ = 0.910) |

*Hazard ratio (HR) and p-values for abnormality versus none (matched)*

Reece D et al. *Blood* 2009;114(3):522-5.

## Discussion

- **The combination of lenalidomide and dexamethasone is an effective therapy for relapsed/refractory MM.**
  - **— Patients with either del(13q) or t(4;14) experienced median TTP and OS comparable to those without the corresponding cytogenetic abnormality.**
- **Patients with del(17p13), however, had significantly worse outcomes (TTP = 2.2 mo; OS = 4.67 mo).**
- **Lenalidomide appears to be ineffective in patients with del(17p13), and novel therapeutic approaches are needed for this subgroup.**

Reece D et al. *Blood* 2009;114(3):522-5.

## *FACULTY COMMENTS*

**DR GIRALT:** This subanalysis of patients participating in the lenalidomide expanded access program shows the influence of cytogenetics on outcome. TTP was 7.1 months for the whole group, but patients with the 17p deletion had a poor prognosis with a TTP of only two months and a median survival of 4.6 months.

Although patients with del(17p) may respond to lenalidomide induction, their overall outcome remains extremely poor, and further investigational strategies are needed for these patients.

Younger patients with these cytogenetic abnormalities could be considered for more aggressive therapies, such as allogeneic transplant.

Another important result of the study is that patients who had the 4;14 translocation had relatively good outcomes with lenalidomide-based therapy, with a median TTP of approximately eight months.

# Safety and Efficacy of Single-Agent Lenalidomide in Patients with Relapsed and Refractory Multiple Myeloma

**Richardson P et al.**

*Blood* 2009;114(4):772-8.

## Introduction

- **Lenalidomide has demonstrated clinical benefit in the treatment of relapsed or refractory multiple myeloma (MM) as monotherapy and in combination with dexamethasone (*Blood* 2002;100:3063; *Blood* 2006;108:3458).**
- **Significant adverse events resulted from the addition of dexamethasone to lenalidomide, including:**
  - **— Deep vein thrombosis, infections and hyperglycemia**
- **<u>Current study objective</u>:**
  - **— Efficacy and safety of single-agent lenalidomide, 30 mg once daily, as therapy for relapsed and refractory MM**
  - **— Primary endpoint: At least partial response**

Richardson P et al. *Blood* 2009;114(4):772-8.

## Phase II Study of Lenalidomide as Treatment for Relapsed and Refractory MM

**Protocol ID: NCT00065351**

| Eligibility (n = 222) |
|---|
| Relapsed and refractory MM |
| Disease progression during or within 60 days of salvage regimen |
| ≥2 prior treatment regimens, not including SCT |

→ **Lenalidomide, 30 mg once daily, d1-21 q 28 days until progression or unacceptable toxicity**

Richardson P et al. *Blood* 2009;114(4):772-8.

## Clinical Response (Intent to Treat)

| | ≤2 Prior Treatment Regimens (n = 73) | ≥3 Prior Treatment Regimens (n = 149) |
|---|---|---|
| CR + PR | 26% | 26% |
| Complete response (CR) | 1% | 3% |
| Partial response (PR) | 25% | 23% |
| Minimal response (MR) | 19% | 17% |
| Stable disease | 48% | 48% |
| Progressive disease | 1% | 5% |

Richardson P et al. *Blood* 2009;114(4):772-8.

## Efficacy (Intent to Treat)

| | Overall (n = 222) | CR + PR (n = 58) | CR + PR + MR (n = 98) |
|---|---|---|---|
| Median PFS (mo) | 4.9* | 14.5 | 10.4 |
| Median TTP (mo) | 5.2† | 14.5 | 10.4 |
| Median OS (mo) | 23.2‡ | 33.9 | 28.0 |
| 1-year survival rate | 67% | 73% | 79% |

** 73% of patients had disease progression or died.*
*† 69% of patients had disease progression.*
*‡ 60% of patients died.*

Richardson P et al. *Blood* 2009;114(4):772-8.

## Discussion

- **Lenalidomide monotherapy at 30 mg/day is an active therapy with long-term benefit in patients with relapsed and refractory MM.**
- **Similar response was obtained in patients who received prior thalidomide, bortezomib or after prior stem cell transplant, respectively.**
  **— ORR = 41%, 46% and 39%, respectively (data not shown)**
- **Toxicity was acceptable. Common Grade 3/4 adverse events were neutropenia (60%), febrile neutropenia (4%), thrombocytopenia (39%) and anemia (20%).**
- **These data support the treatment option of single-agent lenalidomide.**

Richardson P et al. *Blood* 2009;114(4):772-8.

### *FACULTY COMMENTS*

**DR RICHARDSON:** Single-agent lenalidomide at the dose and schedule in this Phase II study showed a robust response rate and impressive PFS and time to disease progression. The median overall survival in this relapsed and refractory population is almost two years, that's quite remarkable, and unprecedented.

Among patients who achieved at least a PR, the survival is approaching three years. The results suggest that if patients respond to this regimen, they can enjoy particularly long disease control.

**DR JAGANNATH:** The study showed that lenalidomide monotherapy at 30 mg/day is an active therapy and that the toxicity is favorable. The drug is effective irrespective of the number of prior therapies.

The PFS is approximately five months, but in those patients who achieved responses, the responses were quite durable in this heavily pretreated group.

The results show that for patients having achieved a response, especially CR or PR, outcomes were improved.

## NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010

## Summary of the Guidelines Update

**National Comprehensive Cancer Network**
**Version 3.2010.**

## Treatments Placed in New Categories: Primary Induction Therapy for Transplant Candidates

| Regimen (supporting trial) | Current category* | Previous category* |
|---|---|---|
| Bortezomib/dexamethasone *(Harousseau et al. ASCO 2008)* | 1 | 2B |
| Bortezomib/doxorubicin/dexamethasone *(Sonneveld et al. ASH 2008)* | 1 | 2B |
| Bortezomib/thalidomide/dexamethasone *(Cavo et al. ASH 2008)* | 1 | 2B |
| Lenalidomide/dexamethasone *(Zonder et al. ASH 2007)* | 1 | 2B |

**Category 1 = uniform consensus, high evidence quality; 2B = nonuniform consensus, lower evidence quality*

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010.

## Treatments Placed in New Categories: Primary Induction Therapy for Transplant Candidates (continued)

| Regimen (supporting trial) | Current category* | Previous category* |
|---|---|---|
| Dexamethasone *(Rajkumar et al.* JCO *2006)* | 2B | 2A |
| Thalidomide/dexamethasone *(Rajkumar et al.* JCO *2006)* | 2B | 2A |
| Liposomal doxorubicin/vincristine/ dexamethasone *(Rifkin et al.* Cancer *2006)* | 2B | 2A |

**Category 2A = uniform consensus, lower evidence quality; 2B = nonuniform consensus, lower evidence quality*

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010.

## Treatments Placed in New Categories: Primary Induction Therapy for Nontransplant Candidates

| Regimen (supporting trial) | Current category | Previous category |
|---|---|---|
| Melphalan/prednisone/thalidomide (MPT) *(Multiple randomized trials compared MPT to MP)* | 1 | 2A |
| Melphalan/prednisone/bortezomib (MPB) *(San Miguel et al.* NEJM *2008 VISTA trial)* | 1 | 2A |
| Lenalidomide/low-dose dexamethasone (Rd) *(Rajkumar et al.* Lancet *2010)* | 1 | 2B |
| Melphalan/prednisone (MP) *(Multiple trials compared MP to either MPT or MPB)* | 2A | 1 |

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010.

## Treatments Placed in New Categories: Primary Induction Therapy for Nontransplant Candidates (continued)

| Regimen (supporting trial) | Current category | Previous category |
|---|---|---|
| Thalidomide/dexamethasone *(Rajkumar et al. JCO 2006)* | 2B | 2A |
| Dexamethasone *(Rajkumar et al. JCO 2006)* | 2B | 2A |
| Vincristine/doxorubicin/dexamethasone (VAD)[1] | 2B | 2A |

*Category 2A: Uniform consensus, lower evidence quality*
*[1] VAD is now category 2B; no specific reference has been cited for the change.*

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010.

## Maintenance Therapy

- **Three independent trials with lenalidomide maintenance have recently reported improvement in disease progression.**
  - **— CALGB-100104: 58% reduction in disease progression (ASH 2009;Abstract 3416.)**
  - **— IFM 2005-02: Improved PFS and sCR/CR (ASH 2009;Abstract 529.)**
  - **— MM-015: 75% reduction in disease progression (ASH 2009;Abstract 613.)**
- **Lenalidomide maintenance added (Category 2A).**
- **Thalidomide alone or with prednisone (Category 1 and 2B respectively).**

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010.

### *FACULTY COMMENTS*

**DR GIRALT:** NCCN guidelines have incorporated the results of multiple Phase III studies for transplant-eligible and transplant-ineligible patients, and the recommendations for initial therapy include regimens containing bortezomib or lenalidomide.

Lenalidomide maintenance studies were presented at ASH 2009. Although not yet published in peer-reviewed journals, these studies are important and should influence practice, and NCCN now acknowledges lenalidomide maintenance therapy in myeloma as an evidence-based option.

**DR ORLOWSKI:** NCCN updates have been made because of the maturation of the major Phase III studies that incorporated novel agents such as bortezomib or lenalidomide in the initial treatment of myeloma.

A number of induction regimens incorporating novel agents have been upgraded in their level of recommendation from IIB to I. NCCN also added lenalidomide maintenance as a category IIA recommendation in view of results presented at ASH from the multitude of studies.

# International Myeloma Working Group Guidelines for the Management of Multiple Myeloma Patients Ineligible for Standard High-Dose Chemotherapy with Autologous Stem Cell Transplantation

**Palumbo A et al.**

*Leukemia* 2009;23(10):1716-30.

## Introduction

- **Prior guidelines were published in 2005.**
- **Current update conducted by a panel of clinical and statistical experts who reviewed articles from 2004-2008 and abstracts from 2006-2008.**
- **No changes to guidances on diagnosis, indications to start therapy or monitoring of myeloma.**
- **Changes in specific areas of multiple myeloma are summarized.**

Palumbo A et al. *Leukemia* 2009;23(10):1716-30.

## Update on Prognostic Factors and Response Criteria

- **Cytogenetics and/or FISH should be performed in all patients at diagnosis and at the time of relapse.**
- **IMWG criteria should be used to assess response (*Leukemia* 2006;20:1467).**
  - **— Response criteria of stringent CR and VGPR have been added.**
  - **— Serum free light chain assay is used to determine stringent CR.**

Palumbo A et al. *Leukemia* 2009;23(10):1716-30.

## Front-Line Therapy

- **IMWG considers MPT and VMP as standard treatment for initial induction therapy in patients ineligible for transplantation and Rd for patients who wish to postpone transplantation.**
- **Major trials reviewed:**
  - **— RD vs Rd (Rajkumar et al. ASCO 2008)**
  - **— MPT vs MP (Palumbo et al. *Blood* 2008)**
  - **— MPT vs MP (Facon et al. *Lancet* 2007)**
  - **— MPT vs MP (Hulin et al. ASH 2007)**
  - **— VMP vs MP (San Miguel et al. *NEJM* 2008)**

Palumbo A et al. *Leukemia* 2009;23(10):1716-30.

## Therapy for Relapsed Myeloma

- **In the relapsed setting, IMWG recommends:**
  - **— Bortezomib with or without dexamethasone or in combination with liposomal doxorubicin**
  - **— Lenalidomide in combination with dexamethasone**
- **Choice of salvage therapy depends on earlier exposure to a particular drug and concomitant comorbidities.**

Palumbo A et al. *Leukemia* 2009;23(10):1716-30.

## Supportive Care In Myeloma

- **Bisphosphonates are recommended in patients with osteolytic lesions.**
  - **— Comprehensive dental examination should be done before starting bisphosphonate therapy.**
  - **— Continue bisphosphonates for two years. However, one year is sufficient for patients in CR/nCR.**
- **Vertebral fracture:**
  - **— Balloon kyphoplasty has shown a marked reduction in back disability and pain in a randomized Phase III trial and should be considered as a standard approach if appropriate (*Clinical Lymphoma Myeloma* 2009;Abstract 204).**

Palumbo A et al. *Leukemia* 2009;23(10):1716-30.

## *FACULTY COMMENTS*

**DR RICHARDSON:** The updated guidelines from IMWG recommend a cytogenetic and/or FISH assay for all patients at diagnosis and at relapse. An additional update was in the determination of the CR quality by use of a serum free light chain assay and the identification of stringent CR.

This update also included incorporating novel agents such as bortezomib, lenalidomide or thalidomide in the initial therapy for transplant-ineligible patients.

**DR ORLOWSKI:** I don't agree with the panel recommendation to perform cytogenetic and/or FISH testing at the time of relapse in transplant-ineligible patients.

I can understand it better for patients who have undergone transplants, because high-dose melphalan can result in chromosomal changes, especially the appearance of 17p abnormalities, but I am not sure that this happens in patients who have not undergone transplants.

Supportive care updates include the use of monthly bisphosphonates for a shorter period than two years for patients who achieve a CR.

# International Myeloma Working Group Molecular Classification of Multiple Myeloma: Spotlight Review

**Fonseca R et al.**

*Leukemia* 2009;23(12):2210-21.

## Introduction

- **Multiple myeloma (MM) is a clonal B-cell disorder with heterogeneity in outcome among different patients.**
- **Several subtypes have been identified at the genetic and molecular level.**
- **Genetic and molecular subtypes are associated with unique clinicopathologic features and have prognostic implications.**

Fonseca R et al. *Leukemia* 2009;23(12):2210-21.

## Genetic Classification

| Hyperdiploid (h) MM | Nonhyperdiploid (nh) MM |
|---|---|
| • 45% of all MM<br>• Numerous chromosome trisomies<br>• More favorable outcome<br>• Slightly more common in males<br>• More common in elderly | • 40% of all MM<br>• Highly enriched for IgH translocations<br>• Overall less favorable outcome<br>• Examples include t(11;14), t(4;14), t(14:16), del(17p) |

*Remaining 15% of MM is either with overlap or unclassified in the two major genetic categories.*

Fonseca R et al. *Leukemia* 2009;23(12):2210-21.

## Molecular Subtypes of MM

- **t(11;14)**
  - **— 15% of all MM**
  - **— Hyposecretory disease**
  - **— Associated with IgM myeloma**
  - **— Prognosis neutral**
- **t(14;16)**
  - **— 5-7% of all MM**
  - **— High prevalence of concomitant chromosome 13 deletion**
  - **— Higher frequency of IgA isotype**
  - **— Aggressive clinical course**

Fonseca R et al. *Leukemia* 2009;23(12):2210-21.

## Molecular Subtypes of MM

- **del(17p13)**
  - **— Most aggressive disease**
  - **— Higher prevalence of extramedullary disease**
  - **— Short duration of response after transplant**
- **t(4;14)**
  - **— 15% of all MM**
  - **— High prevalence of concomitant chromosome 13 abnormalities**
  - **— Poor outcome**
  - **— Bortezomib may overcome the poor prognosis of this subgroup**

Fonseca R et al. *Leukemia* 2009;23(12):2210-21.

## Molecular Subtypes of MM

- Chromosome 13 abnormalities
  - — Present in 50% of MM and 90% of t(4;14) and t(14;16)
  - — Significance is considered as of surrogate association with nh MM
- Chromosome 1 abnormalities
  - — Emerging marker
  - — Negative prognostic association in some reports

Fonseca R et al. *Leukemia* 2009;23(12):2210-21.

## Gene Expression Profiling

- University of Arkansas and IFM (Intergroupe Francophone du Myélome) have identified gene signatures that can provide prognostic discrimination.
- There is minimal overlap between these two signatures, and both will need validation.
- It is conceivable that gene signatures may become predictive markers in the future.

Fonseca R et al. *Leukemia* 2009;23(12):2210-21.

## Summary and Recommendations

- Baseline genetic information should be obtained in all MM cases.
- FISH testing must be done on purified plasma cells and not on unsorted samples.
- Minimal panel required for prognostication should include t(4;14), t(14;16) and del(17p13).
- A more comprehensive panel should include testing for t(11;14), chromosome 13 deletion, ploidy category and chromosome 1 abnormalities.
- Gene expression signatures should be incorporated in all clinical trials.

Fonseca R et al. *Leukemia* 2009;23(12):2210-21.

## *FACULTY COMMENTS*

**DR GIRALT:** The classification of myeloma using a variety of cytogenetic abnormalities as documented by conventional cytogenetics or FISH is becoming an accepted practice.

It is important to note that although no specific treatments have been devised for myeloma in patients with specific cytogenetic abnormalities, more and more data suggest that these abnormalities could be amenable to specific targeted therapies in the future.

This review article describes various myeloma-associated specific molecular abnormalities as distinct entities and divides them into two major subtypes. None of the clinical features described are specific enough to make the diagnosis clinically.

Currently they have prognostic significance, and some of them may become predictive markers for specific therapies in the future.

The panel recommends that all patients with newly diagnosed multiple myeloma should undergo cytogenetic analysis and FISH analysis for t(4;14), t(14;16), t(11;14) and del 17p.

# International Myeloma Working Group Guidelines for Serum-Free Light Chain Analysis in Multiple Myeloma and Related Disorders

**Dispenzieri A et al.**

*Leukemia* 2009;23(2):215-24.

## Introduction

- **Serum free light chain (FLC) assay was developed in early 2000s.**
- **Assay consists of quantitating circulating free κ and λ light chain immunoglobulin as well as providing κ/λ FLC ratio (rFLC).**
- **This review describes uses in which FLC has proven its utility and areas in which it is still investigational.**

Dispenzieri A et al. *Leukemia* 2009;23(2):215-24.

## Screening for Plasma Cell Disorders

**Gold standard for plasma cell disorders screening is immunofixation electrophoresis (IFE) of serum and urine.**

**A prior study identified 428 patients in the Mayo Clinic database who had positive urinary IFE (u IFE) and also had serum IFE (sIFE), serum protein electrophoresis (SPEP) and serum rFLC done (*Mayo Clin Proc* 2006;81:1575).**

| Laboratory test | % Abnormal | % Missed if urinary IFE was not done |
|---|---|---|
| sIFE or SPEP | 93.5 | 6.5 |
| sIFE or rFLC | 99.5 | 0.5 |

Dispenzieri A et al. *Leukemia* 2009;23(2):215-24.

## Prognostic Value of Serum FLC Assay

- **MGUS/Smoldering Myeloma/Solitary Plasmacytoma: Abnormal rFCL is an independent predictor for higher rate of progression.**
- **Multiple Myeloma: Highly abnormal rFLC (<0.03 or >32) predicts inferior outcomes when compared to those with less severe abnormality (*Leukemia* 2008;22:1933).**
- **Amyloidosis: Baseline FLC correlates with the risk of death (*Blood* 2006;107:3378).**

Dispenzieri A et al. *Leukemia* 2009;23(2):215-24.

## Monitoring and Response Assessment with Serum FLC Assay

- **Amyloidosis:**
  - **— FLC response has been shown to correlate with survival (*BJH* 2003;122:78).**
- **Oligosecretory myeloma/light chain deposition disease:**
  - **— No data suggest that FLC changes correlate with disease status or outcome.**
    - **– However, anecdotal reports exist in the literature to support a role of FLC in this population, and authors confirm their personal experience of use in follow-up of such patients.**

Dispenzieri A et al. *Leukemia* 2009;23(2):215-24.

## Monitoring and Response Assessment with Serum FLC Assay (continued)

- **Active Multiple Myeloma:**
  - **There is no data to suggest routine use except to document stringent CR in a patient who has already attained CR.**
    - **FLC half-life is 2 to 4 hours, while that of IgG is 8 to 21 days.**
    - **FLC may detect an early response or an early relapse.**
    - **No data is currently available to show that early detection of response or relapse may change the patient's outcome.**

Dispenzieri A et al. *Leukemia* 2009;23(2):215-24.

## Summary and Recommendations

- **Serum FLC assay in combination with serum IFE is sufficient for screening plasma cell disorders.**
- **Serum FLC assay should be measured at diagnosis for prognostic purposes for all plasma cell disorders.**
- **Serum FLC assay should be conducted in the follow-up of patients with amyloidosis, oligosecretory myeloma and light chain-only myeloma and should also be conducted in patients with active multiple myeloma who have achieved a CR to determine a stringent CR.**

Dispenzieri A et al. *Leukemia* 2009;23(2):215-24.

### *FACULTY COMMENTS*

**DR RICHARDSON:** This is a useful article that provides guidance on the use of free light chain (FLC) assays. In combination with serum immunofixation, FLC is highly sensitive and can replace 24-hour urine studies in screening for plasma cell disorders.

Baseline FLC has major prognostic value in virtually every plasma cell disorder, and finally, it allows monitoring of patients with oligosecretory myeloma or monitoring to determine the quality of CR in patients with myeloma.

**DR JAGANNATH:** The assay quantitates the serum light chains that are circulating independent of the heavy chains. It could be used in various clinical scenarios and, most importantly, it has prognostic value for all plasma cell disorders.

Currently FLC has no value in the routine monitoring of active multiple myeloma. However, it makes it easier to follow patients with oligosecretory myeloma, amyloidosis or light chain disease, and it should be used in those settings.

## The Use of Bisphosphonates in Multiple Myeloma: Recommendations of an Expert Panel on Behalf of the European Myeloma Network

**Terpos E et al.**

*Ann Oncol* 2009;20(8):1303-17.

## Introduction

- **Bone destruction occurs in 90% of patients with MM (*Oncologist* 2007;12:62).**
- **Bisphosphonates have become the standard of care in MM to reduce and delay the skeletal morbidity.**
- **Recommendations developed by an expert panel after multiple rounds of review of associated evidence are summarized.**

Terpos E et al. *Ann Oncol* 2009;20(8):1303-17.

## Major Double Blind Trials of Bisphosphonates in MM

| Bisphosphonate/ Control | Manuscript | N | Reduction of pain | Reduction of skeletal related events (SRE) |
|---|---|---|---|---|
| Pamidronate (IV) vs Placebo | *JCO* 1998;16:593 | 392 | Yes | Yes |
| Zoledronic Acid (IV) vs Pamidronate (IV) | *Cancer* 2001;91:1191 | 108 | Yes | Yes |
| Zoledronic Acid (IV) vs Pamidronate (IV) | *Cancer* 2003;98:1735 | 513 | Yes | Yes |

Terpos E et al. *Ann Oncol* 2009;20(8):1303-17.

## Renal Impairment with Bisphosphonates

- Serum creatinine should be monitored before each dose.
- Patients with renal impairment should have creatinine clearance rates, serum electrolytes and albuminuria also monitored.
  - — Moderate renal impairment (creatinine clearance 30-60 mL/min):
    - – Lower doses and longer infusions of pamidronate
    - – Lower doses with no changes in infusion time with zoledronic acid
  - — Severe renal impairment (creatinine clearance < 30 mL/minute): Should not receive bisphosphonates

Terpos E et al. *Ann Oncol* 2009;20(8):1303-17.

## Osteonecrosis of Jaw (ONJ) with Bisphosphonates

- Preventive dentistry with ongoing dental evaluation has shown a 75% reduction in ONJ (*Annals of Oncology* 2009;20:137).
- A comprehensive dental examination should be done before initiating bisphosphonates.
- Existing/high-risk dental conditions should be treated before starting bisphosphonates.
- Bisphosphonates should be stopped if a patient develops ONJ.

Terpos E et al. *Ann Oncol* 2009;20(8):1303-17.

## Summary

- Bisphosphonates should be administered to patients with MM with osteolytic lesions or osteopenia.
  - — Bisphosphonates should be continued for 2 years, and administration beyond 2 years is not recommended.
- After 2 years, bisphosphonates should be reinitiated in patients with pain or documented progression in bone involvement.
- Patients with MGUS, asymptomatic multiple myeloma or solitary plasmacytoma should not receive bisphosphonates.

Terpos E et al. *Ann Oncol* 2009;20(8):1303-17.

## *FACULTY COMMENTS*

**DR GIRALT:** The European Myeloma Network convened an expert panel to discuss the use of bisphosphonates for patients with multiple myeloma. The panel recommends continuing bisphosphonates for two years for most patients with myeloma and emphasizes the need for initial and ongoing renal and dental evaluation in patients receiving bisphosphonates.

**DR JAGANNATH:** Not all experts will agree that administration of bisphosphonates beyond two years is not to be recommended. Evidence for benefit beyond two years may be difficult to generate in this setting, and a less frequent bisphosphonate administration might be considered.

In contrast, if a patient has attained CR after therapy with novel agents or transplant, he or she has no need to continue monthly therapy for two years.

My opinion, and that endorsed by the IMWG, is that frequency of administration could be reduced after less than two years for patients attaining CR.

# Pomalidomide (CC4047) Plus Low-Dose Dexamethasone as Therapy for Relapsed Multiple Myeloma

**Lacy MQ et al.**

*J Clin Oncol* 2009;27(30):5008-14.

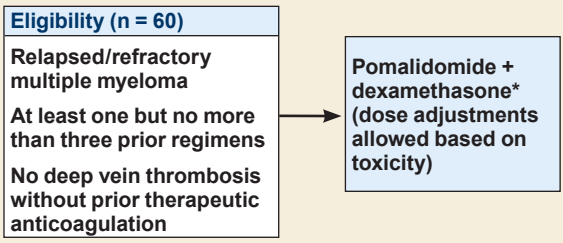
## Introduction

- **A curative therapy for multiple myeloma (MM) does not exist and most patients relapse.**
- **Pomalidomide is a new immunomodulatory drug demonstrated to be highly potent in vitro (*Blood* 2006;107:3098; *Leukemia* 2003;17:41).**
- **Pomalidomide dosed from 1 to 5 mg/mL has been shown to be well tolerated in Phase I trials in patients with relapsed MM (*Br J Haematol* 2008;141:41).**
- **Current study objective:**
  - **— Assess the efficacy and safety of pomalidomide plus dexamethasone therapy for patients with relapsed MM.**

Lacy MQ et al. *J Clin Oncol* 2009;27(30):5008-14.

## Phase II Trial of Pomalidomide Plus Low-Dose Dexamethasone in Patients with Relapsed Multiple Myeloma

**Protocol ID: NCT00558896**




**Pomalidomide 2 mg/day oral, d1-28 q28 days*
*Dexamethasone 40 mg/day oral, d1, 8, 15, 22 q28 days*

Lacy MQ et al. *J Clin Oncol* 2009;27(30):5008-14.

## Confirmed Responses in Patients with Refractory Disease

| Response | CR | VGPR | PR | RR |
|---|---|---|---|---|
| Total population (n = 60) | 5% | 28% | 30% | 63% |
| Bortezomib refractory (n = 10) | 10% | 20% | 30% | 60% |
| Lenalidomide refractory (n = 20) | 0% | 5% | 35% | 40% |
| Bortezomib and lenalidomide refractory (n = 5) | 0% | 20% | 40% | 60% |

*CR = complete response; VGPR = very good partial response; PR = partial response; RR = response rate (CR + VGPR + PR)*

Lacy MQ et al. *J Clin Oncol* 2009;27(30):5008-14.

## Confirmed Responses in Patients at High Risk

| Response | CR | VGPR | PR | RR |
|---|---|---|---|---|
| All high risk* (n = 19) | 5% | 27% | 42% | 74% |
| Deletion 13 (n = 4) | 0% | 25% | 75% | 100% |
| t(14;16) (n = 3) | 0% | 0% | 67% | 67% |
| 17p- (n = 5) | 0% | 60% | 40% | 100% |
| PCLI ≥ 3% (n = 8) | 12.5% | 25% | 25% | 63% |

*Only one patient with t(14;16) achieved stable disease.*
**Two patients had two high-risk factors; PCLI = plasma cell labeling index*

Lacy MQ et al. *J Clin Oncol* 2009;27(30):5008-14.

## Conclusions

- **The pomalidomide plus low-dose dexamethasone combination was highly active as a treatment for relapsed/refractory MM.**
  - **— RR in patients with refractory MM: 63%**
  - **— RR in patients with high-risk MM: 74%**
- **Toxicity was mild and consisted mainly of Grade 3/4 neutropenia (data not shown).**
- **Additional Phase II trials are planned with this treatment combination to better define response rates in patients with lenalidomide- and bortezomib-refractory MM.**

Lacy MQ et al. *J Clin Oncol* 2009;27(30):5008-14.

### *FACULTY COMMENTS*

**DR GIRALT:** Pomalidomide is a new immunomodulator that is highly potent in vitro against multiple myeloma and is evaluated in this Phase II study in combination with low-dose dexamethasone.

The combination is highly active in relapsed myeloma, and responses are observed across the board, even in patients who had experienced progression on lenalidomide and bortezomib combinations and in those with high-risk disease by cytogenetics. Toxicity is mild and consists mainly of Grade III or IV neutropenia.

**DR ORLOWSKI:** Pomalidomide was administered once a day with weekly dexamethasone and with aspirin for thromboprophylaxis. Of 60 patients who were enrolled, 38 patients or 63 percent achieved a response.

Responses were observed in 40 percent of patients with lenalidomide-refractory disease and 60 percent of patients with disease that was refractory to both bortezomib and lenalidomide. This will be a great drug to have in the relapsed and/or refractory setting after therapy with bortezomib or one of the other immunomodulatory drugs.

## PX-171-004, an Ongoing Open-Label Phase II Study of Single-Agent Carfilzomib (CFZ) in Patients with Relapsed or Refractory Myeloma (MM): Updated Results from the Bortezomib-Treated Cohort

**Siegel D et al.**

*Proc ASH* 2009;Abstract 303.

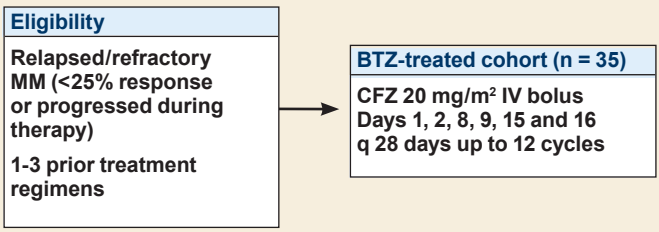
## Introduction

- **CFZ may provide greater, more sustained proteasomal inhibition than bortezomib (BTZ):**
  - **— CFZ overcomes BTZ resistance in vitro (*Blood* 2007;110:3281).**
  - **— Durable responses and disease control were observed in a Phase II study for progressive MM (ASCO 2009;Abstract 8504).**
- **<u>Current study objective</u>:**
  - **— Evaluate patient responses by IMWG criteria from the bortezomib-treated cohort of the PX-171-004 study**
  - **— Primary objective: Overall response rate (ORR), defined as ≥partial response**

Siegel D et al. *Proc ASH* 2009;Abstract 303.

## Phase II Study of CFZ for Relapsed or Refractory MM (BTZ-Treated Cohort)

**Protocol ID: PX-171-004**




Siegel D et al. *Proc ASH* 2009;Abstract 303.

## Efficacy of CFZ Therapy in BTZ-Treated Cohort (n = 33*)

| | |
|---|---|
| Complete response | 1 (3%) |
| Very good partial response | 1 (3%) |
| Partial response (PR) | 4 (12%) |
| Minimal response (MR) | 4 (12%) |
| Stable disease ≥6 weeks | 13 (39%) |
| ORR (≥PR) = 18%; CBR (≥MR) = 30%; disease control = 70% | |

*Duration of ≥MR = 9.0 mo; duration of ≥PR = 10.6 mo*
*Median TTP = 5.3 mo at 11.5-month follow-up; * Evaluable patients*

Siegel D et al. *Proc ASH* 2009;Abstract 303.

## Select ≥Grade 3 Adverse Events*

| | |
|---|---|
| Anemia | 5 (14%) |
| Neutropenia | 4 (11%) |
| Thrombocytopenia | 2 (6%) |
| Pneumonia | 2 (6%) |
| Dyspnea | 2 (6%) |
| Upper respiratory infection | 2 (6%) |

** Includes related and nonrelated Grade 3 or 4 events in >5% of patients*

Siegel D et al. *Proc ASH* 2009;Abstract 303.

## Conclusions

- **CFZ (20 mg/m$^2$) achieves durable responses and disease control in patients with MM despite prior bortezomib treatment.**
  - **— 18% ORR; 70% disease control; TTP = 5.3 mo**
- **Adverse events are mild and manageable.**
  - **— Tolerability permits long-term treatment — 23% completed 12 cycle protocol (~ 1 year therapy; data not shown).**
  - **— Peripheral neuropathy is rare, mild and does not limit therapy despite preexisting symptoms (data not shown).**
- **These data support the continuing evaluation of CFZ as a treatment option for MM.**
  - **— Ongoing Phase II trial (PX-171-003 A1, n = 269) is further studying this agent in relapsed and refractory MM.**

Siegel D et al. *Proc ASH* 2009;Abstract 303.

### *FACULTY COMMENTS*

**DR GIRALT:** Another new agent that we hope will come soon to the clinic is carfilzomib. These data suggest that single-agent carfilzomib is well tolerated and effective in patients who have experienced progression on prior bortezomib.

It will be an important addition to our clinical armamentarium against relapsed and refractory multiple myeloma.

**DR ORLOWSKI:** Carfilzomib is a second-generation proteasome inhibitor and causes irreversible proteasome inhibition as bortezomib causes reversible proteasome inhibition. The data presented are from a cohort of patients who had relapsed or refractory disease. The median number of prior regimens was three: All had received bortezomib therapy and 77 percent had received lenalidomide or thalidomide.

The overall response rate was 18 percent in this heavily pretreated group, and the median duration of response was 10.6 months. The neuropathy rate was low with no Grade IV neuropathy and Grade III neuropathy in only 2.9 percent of the patients.

## PRIORITY 2 PUBLICATIONS/PRESENTATIONS (RECOMMENDED)

### UP-FRONT/INDUCTION THERAPY

1 Dimopoulos MA et al. **VMP (bortezomib, melphalan, and prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: Cohort analysis of the phase III VISTA study.** J Clin Oncol 2009;27(36):6086-93.

*Among patients with myeloma and moderate renal impairment, addition of bortezomib to MP as initial therapy is a safe and effective approach that reverses renal insufficiency in a substantial proportion (44 percent) of patients.*

2 Hulin C et al. **Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial.** J Clin Oncol 2009;27(22):3664-70.

*The MPT regimen demonstrates acceptable toxicity and superior overall survival (44 months) when compared to MP (29 months) in elderly (>75 years) patients with multiple myeloma.*

3 Ludwig H et al. **Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma.** Blood 2009;113(15):3435-42.

*High-dose dexamethasone in combination with thalidomide is associated with significant toxicities and poorer survival for patients who are elderly or with poor performance status and thus a less aggressive approach is more appropriate.*

4 Harousseau J-L et al. **Bortezomib plus dexamethasone (VD) versus reduced-dose bortezomib plus thalidomide plus dexamethasone (vTD) as induction treatment prior to autologous stem-cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM).** Proc ASH 2009;Abstract 354.

*The combination of reduced-dose bortezomib and thalidomide with dexamethasone results in minimal peripheral neuropathy (Grade ≥III = 2 percent) and induces significantly more responses (50 percent ≥VGPR) than VD (30 percent ≥VGPR).*

5 Jakubowiak AJ et al. **Phase II trial of combination therapy with bortezomib, pegylated liposomal doxorubicin, and dexamethasone in patients with newly diagnosed myeloma.** J Clin Oncol 2009;27(30):5015-22.

*Acceptable safety and promising efficacy (57.5 percent ≥VGPR) are seen in newly diagnosed myeloma with bortezomib, pegylated liposomal doxorubicin and dexamethasone combination therapy.*

6 Hussein MA et al. **Phase II study of thalidomide plus dexamethasone induction followed by tandem melphalan-based autotransplantation and thalidomide-plus-prednisone maintenance for untreated multiple myeloma: A Southwest Oncology Group trial (S0204).** J Clin Oncol 2009;27(21):3510-7.

*Tandem transplantation is feasible and shows improved VGPR rates and survival outcomes when compared to a matched cohort receiving single transplants or chemotherapy without transplantation.*

7 Kapoor P et al. **Melphalan and prednisone (MP) versus melphalan, prednisone and thalidomide (MPT) as initial therapy for previously untreated elderly and/or transplant ineligible patients with multiple myeloma: A meta-analysis of randomized controlled trials.** Proc ASH 2009;Abstract 615.

*A meta-analysis of four randomized controlled trials for elderly and/or transplant-ineligible patients with myeloma confirms that MPT is significantly superior to MP as initial therapy with respect to response rates and overall survival.*

8 Palumbo AP et al. **A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients.** Proc ASCO 2009;Abstract 8515.

*Among elderly patients with newly diagnosed myeloma, the combination of thalidomide with VMP, using weekly bortezomib dosing, improves response rates (≥VGPR 55 percent versus 45 percent) without an increase in peripheral neuropathy.*

9 Attal M et al. **Lenalidomide after autologous transplantation for myeloma: First analysis of a prospective, randomized study of the Intergroupe Francophone Du Myelome (IFM 2005 02).** Proc ASH 2009;Abstract 529.

*An interim analysis including only the lenalidomide-consolidation data after transplant showed that response was upgraded with consolidation in 15 percent of patients. Results from the lenalidomide-maintenance phase are not yet available.*

10 Spencer A et al. **Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure.** J Clin Oncol 2009;27(11):1788-93.

*Among patients receiving transplants, thalidomide/prednisolone consolidation for 12 months improves three-year survival (86 percent versus 75 percent) with an increased incidence of peripheral neuropathy (0 percent to 10 percent ≥Grade III).*

11 Mellqvist U-H et al. I**mproved response rate with bortezomib consolidation after high dose melphalan: First results of a Nordic Myeloma Study Group randomized Phase III trial.** Proc ASH 2009;Abstract 530.

*Bortezomib consolidation for 21 weeks after transplant shows improvement in responses (CR/nCR 54 percent versus 35 percent) and in six-month relapse rate (one percent versus six percent) in this placebo-controlled study.*

12 Loiseau HA et al. **Induction with Velcade®/dexamethasone partially overcomes the poor prognosis of t(4;14), but not that of Del(17p), in young patients with multiple myeloma.** Proc ASH 2009;Abstract 957.

*A retrospective analysis shows that the outcome (PFS and OS) for patients with t(4;14) is partially improved with bortezomib/dexamethasone induction therapy, although this combination does not improve the outcome for patients with del(17p).*

13 Dawson MA et al. **Clinical and immunohistochemical features associated with a response to bortezomib in patients with multiple myeloma.** Clin Cancer Res 2009;15(2):714-22.

*A prior complete response with an alternative drug and cyclin D1 expression are associated with an improved response to bortezomib, while expression of p16, cytoplasmic p53 and high Bcl-2 staining is associated with a poor response.*

## STEM CELL HARVESTING/AUTO, ALLO AND MINI-ALLO TRANSPLANTS

14 DiPersio JF et al, on behalf of the 3102 Investigators. **Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma.** Blood 2009;113(23):5720-6.

*For patients with myeloma, a mobilization regimen of plerixafor and G-CSF results in a significantly improved ability to achieve optimal CD34+ cell targeting for tandem transplantation in fewer apheresis procedures compared to G-CSF alone.*

15 Stiff P et al. **Treatment with plerixafor in non-Hodgkin's lymphoma and multiple myeloma patients to increase the number of peripheral blood stem cells when given a mobilizing regimen of G-CSF: Implications for the heavily pretreated patient.** Biol Blood Marrow Transplant 2009;15(2):249-56.

*A combination of plerixafor and G-CSF is safe and effective in mobilizing stem cells in patients with heavily pretreated non-Hodgkin lymphoma or multiple myeloma.*

16 Giralt S et al, on behalf of the IMWG. **International Myeloma Working Group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100).** Leukemia 2009;23(10):1904-12.

*G-CSF alone is reasonable for stem cell collection in myeloma. Plerixafor should be considered as part of the mobilization regimen for patients who have risk factors such as age >60, extensive prior therapy or prolonged disease duration.*

## RELAPSED/REFRACTORY DISEASE

17 Richardson PG et al. **Multicenter, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and relapsed/refractory multiple myeloma.** J Clin Oncol 2009;27(34):5713-9.

*For patients with relapsed/refractory myeloma, the combination of lenalidomide and bortezomib is safe and is associated with promising activity evident in a median survival of 37 months and a minimal or better response rate of 61 percent.*

18 Stadtmauer EA et al. **Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma.** Eur J Haematol 2009;82(6):426-32.

*A greater benefit in response rates and survival (42.0 months versus 35.8 months, p = 0.041) occurs when lenalidomide/dexamethasone therapy is administered at first relapse rather than later as salvage therapy for patients with relapsed or refractory myeloma.*

19 Knop S et al. **Lenalidomide, Adriamycin, and dexamethasone (RAD) in patients with relapsed and refractory multiple myeloma: A report from the German Myeloma Study Group DSMM (Deutsche Studiengruppe Multiples Myelom).** Blood 2009;113(18):4137-43.

*Addition of doxorubicin to the RD regimen induces substantial remission (73 percent OR and 61 percent ≥VGPR) in heavily pretreated myeloma. Side effects are manageable and are mainly hematologic.*

20 Petrucci MT. **Efficacy and safety of retreatment with bortezomib in patients with multiple myeloma: Interim results from RETRIEVE, a prospective international Phase 2 study.** Proc ASH 2009;Abstract 3866.

*Among patients with relapsed myeloma who had responded previously to bortezomib, re-treatment was safe and active with an overall response rate of 40 percent.*

21 Dimopoulos MA et al. **Treatment of patients with relapsed/refractory multiple myeloma (MM) with lenalidomide and dexamethasone with or without bortezomib: Prospective evaluation of the impact of cytogenetic abnormalities.** Proc ASH 2009;Abstract 958.

*The addition of bortezomib to lenalidomide/dexamethasone may overcome to a certain extent the adverse prognosis of the cytogenetic abnormalities t(4;14), del(13q) and add1q21 but not that of del(17p).*

## TREATMENT-RELATED SIDE EFFECTS/SUPPORTIVE CARE

22 Zangari M et al. **Survival effect of venous thromboembolism in patients with multiple myeloma treated with lenalidomide and high-dose dexamethasone.** J Clin Oncol 2010;28(1):132-5.

*Lenalidomide/high-dose dexamethasone is associated with an increased incidence of venous thromboembolism (17 percent) in relapsed or refractory myeloma, but no effect on survival or time to disease progression was associated with this adverse event.*

23 Vij R et al. **An open-label, phase 2 trial of denosumab in the treatment of relapsed or plateau-phase multiple myeloma.** Am J Hematol 2009;84(10):650-6.

*Denosumab appears safe and active, with 21 percent of patients whose multiple myeloma relapsed less than three months before study entry maintaining stable disease up to 16.5 months and 46 percent of patients with plateau-phase myeloma maintaining stable disease up to 18.3 months.*

24 Katz J et al. **Bisphosphonate-induced osteonecrosis of the jaw: Long-term outcomes.** J Support Oncol 2009;7(1):9-10.

*This retrospective analysis suggests that bisphosphonate-induced osteonecrosis of the jaw is reversible in most cases after discontinuation of the bisphosphonate and becomes asymptomatic with minimal dental intervention.*

## INVESTIGATIONAL AGENTS

25 Richardson P et al. **A Phase 1/2 multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose, safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib.** Proc ASH 2009;Abstract 301.

*Pomalidomide is an active agent in heavily pretreated myeloma and shows a low incidence of neuropathy, thromboembolism, somnolence or constipation, with myelosuppression being the most common adverse event.*

26 Niesvizky R et al. **Phase Ib multicenter dose escalation study of carfilzomib plus lenalidomide and low dose dexamethasone (CRd) in relapsed and refractory multiple myeloma (MM).** Proc ASH 2009;Abstract 304.

*Among patients with relapsed or refractory myeloma, a carfilzomib/lenalidomide/low-dose dexamethasone combination has shown promising activity without dose-limiting toxicities. A Phase III trial is now planned to compare CRd to Rd.*

27 Wang L et al. **Updated results of bortezomib-naïve patients in PX-171-004, an ongoing open-label, Phase II study of single-agent carfilzomib (CFZ) in patients with relapsed or refractory myeloma (MM).** Proc ASH 2009;Abstract 302.

*Single-agent carfilzomib is active (OR = 45 percent) in relapsed or refractory myeloma, with infrequent peripheral neuropathy (Grade III = two percent) and relatively uncommon myelosuppression.*

## MGUS/SMOLDERING MYELOMA

28 Mateos M-V et al. **Multicenter, randomized, open-label, Phase III trial of lenalidomide-dexamethasone (len-dex) vs therapeutic abstention in smoldering multiple myeloma at high risk of progression to symptomatic MM: Results of the first interim analysis.** Proc ASH 2009;Abstract 614.

*High-risk smoldering myeloma is associated with a substantial risk of early progression to symptomatic myeloma. Lenalidomide/dexamethasone can result in high response rates and a significant delay in disease progression.*

29 Rossi F et al. **Proposal and validation of prognostic scoring systems for IgG and IgA monoclonal gammopathies of undetermined significance.** Clin Cancer Res 2009;15(13):4439-45.

*Clinicohematologic features of 1,283 patients with MGUS were correlated with evolution into myeloma. IgA class, serum M protein levels and light-chain proteinuria are the most important variables correlated with disease progression.*

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Attal M et al. **Maintenance therapy with thalidomide improves survival in patients with multiple myeloma.** *Blood* 2006;108(10):3289-94.

Avet-Loiseau H et al. **Genetic abnormalities and survival in multiple myeloma: The experience of the Intergroupe Francophone du Myelome.** *Blood* 2007;109(8):3489-95.

Cavo M et al. **Superior complete response rate and progression-free survival after autologous transplantation with up-front Velcade-thalidomide-dexamethasone compared with thalidomide-dexamethasone in newly diagnosed multiple myeloma.** *Blood* 2008;112;Abstract 158.

Dimopoulos M et al. **Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma.** *N Engl J Med* 2007;357(21):2123-32.

Dispenzieri A et al. **Absolute values of immunoglobulin free light chains are prognostic in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation.** *Blood* 2006;107(8):3378-83.

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Gay F et al. **Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: A comparative analysis of 411 patients.** *Blood* 2010;115(7):1343-50.

Gridelli C. **The use of bisphosphonates in elderly cancer patients.** *Oncologist* 2007;12(1):62-71.

Harousseau JL et al. **Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): Updated data from IFM 2005/01 trial.** *Proc ASCO* 2008;Abstract 8505.

Hulin C et al. **Melphalan-prednisone-thalidomide (MP-T) demonstrates a significant survival advantage in elderly patients 75 years with multiple myeloma compared with melphalan-prednisone (MP) in a randomized, double-blind, placebo-controlled trial, IFM 01/01.** *Blood* 2007;110;Abstract 75.

Katzmann JA et al. **Elimination of the need for urine studies in the screening algorithm for monoclonal gammopathies by using serum immunofixation and free light chain assays.** *Mayo Clin Proc* 2006(12);81:1575-8.

Lachmann HJ et al. **Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy.** *Br J Haematol* 2003;122(1):78-84.

Lentzsch S et al. **Immunomodulatory analogs of thalidomide inhibit growth of Hs Sultan cells and angiogenesis in vivo.** *Leukemia* 2003;17(1):41-4.

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Mateos MV et al. **Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: Results of a multicenter phase 1/2 study.** *Blood* 2006;108(7):2165-72.

McCarthy PL et al. **Phase III Intergroup study of lenalidomide (CC-5013) versus placebo maintenance therapy following single autologous stem cell transplant for multiple myeloma (CALGB 100104): Initial report of patient accrual and adverse events.** *Proc ASH* 2009;Abstract 3416.

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Palumbo A et al. **Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: Updated results of a randomized controlled trial.** *Blood* 2008;112(8):3107-14.

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Snozek CL et al. **Prognostic value of the serum-free light chain ratio in patients with newly diagnosed myeloma and proposed incorporation into the International Staging System.** *Leukemia* 2008;22(10):1933-7.

Sonneveld P et al. **First analysis of HOVON-65/GMMG-HD4 randomized Phase III trial comparing bortezomib, Adriamycin, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM).** *Blood* 2008;112;Abstract 653.

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Zonder JA et al. **Superiority of lenalidomide (len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): Results of the randomized, double-blinded, placebo-controlled SWOG Trial S0232.** *Blood* 2007;110;Abstract 77.

# Post-Test

**QUESTIONS (PLEASE CIRCLE ANSWER):**

1. **Progression-free survival was significantly improved for patients receiving VTD versus TD incorporated into a double autotransplantation regimen.**
   a. True
   b. False
2. **Achieving at least a very good partial response after induction therapy appeared to be a prognostic factor for improved _____ according to the Phase III trial results of Harousseau and colleagues.**
   a. Overall survival
   b. Complete response rate
   c. Progression-free survival
3. **Pomalidomide with low-dose dexamethasone resulted in a response rate of approximately _____ among patients with relapsed or refractory multiple myeloma with high-risk cytogenetics.**
   a. 15 percent
   b. 40 percent
   c. 75 percent
   d. 100 percent
4. **Administration of continuous lenalidomide in patients with newly diagnosed multiple myeloma was shown to be superior to regimens of limited lenalidomide duration.**
   a. True
   b. False
5. **Which of the following increases the risk of bortezomib-associated neuropathy for patients with multiple myeloma?**
   a. Prior treatment with vincristine
   b. Prior treatment with thalidomide
   c. History of diabetes
   d. All of the above
   e. None of the above
6. **Which of the following is not correct if the bortezomib dose/schedule is modified after development of ≥Grade II neuropathy in patients with multiple myeloma?**
   a. Dose modification leads to amelioration of neuropathy
   b. Dose modification adversely affects the efficacy outcome
   c. Dose modification does not adversely affect the efficacy outcome
7. **Which of the following is correct regarding cytogenetics and/or FISH testing for patients with multiple myeloma?**
   a. Only patients who have extramedullary disease should undergo cytogenetics and/or FISH testing
   b. Only patients with IgM or IgA subtypes should undergo cytogenetics and/or FISH testing
   c. All patients with multiple myeloma should undergo cytogenetics and/or FISH testing
8. **Which of the following is correct regarding the NCCN recommendations for maintenance lenalidomide in patients with multiple myeloma?**
   a. NCCN has added maintenance lenalidomide as a category 2A recommendation for transplant candidates only
   b. NCCN has added maintenance lenalidomide as a category 2A recommendation for transplant-ineligible patients only
   c. NCCN has added maintenance lenalidomide for all patients with myeloma regardless of their transplant eligibility
   d. NCCN does not recommend maintenance lenalidomide for patients with myeloma
9. **In a randomized trial for patients older than age 65 with untreated multiple myeloma, induction therapy with bortezomib/melphalan/prednisone resulted in higher response rates than bortezomib/thalidomide/prednisone.**
   a. True
   b. False
10. **In the MM-016 expanded access program study for patients with relapsed or refractory multiple myeloma, treatment with lenalidomide and dexamethasone was relatively ineffective in patients with the _____ cytogenetic abnormality.**
    a. del(13q)
    b. t(4:14)
    c. del(17p13)
    d. All of the above
11. **As initial therapy for newly diagnosed multiple myeloma, lenalidomide with low-dose dexamethasone resulted in a higher overall response rate, increased overall survival and lower toxicity than lenalidomide with high-dose dexamethasone.**
    a. True
    b. False
12. **In a Phase II study for patients with relapsed or refractory multiple myeloma, treatment with single-agent lenalidomide 30 mg/day resulted in a median progression-free survival of _____ months and overall survival of ____ months.**
    a. Two, 10
    b. Five, 23
    c. 10, 15
    d. Five, 12
13. **Which of the following is improved with VMP as initial therapy compared to MP for patients with myeloma?**
    a. Overall survival
    b. Time to next treatment
    c. Treatment-free interval
    d. All of the above
14. **VMP results in improved survival compared to MP in which of the following subsets of patients with myeloma?**
    a. Patients <75 years old
    b. Patients receiving subsequent therapy
    c. Both a and b

*Post-test answer key: 1a, 2c, 3c, 4a, 5e, 6b, 7c, 8c, 9b, 10c, 11b, 12b, 13d, 14c*

# Educational Assessment and Credit Form

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

**Please tell us about your experience with this educational activity**

**How would you characterize your level of knowledge on the following topics?**

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

| | Before | After |
|---|---|---|
| Incorporation of bortezomib- and IMiD®-based regimens into the treatment of newly diagnosed multiple myeloma | 4 3 2 1 | 4 3 2 1 |
| Adverse cytogenetics and response to bortezomib- and IMiD-based regimens | 4 3 2 1 | 4 3 2 1 |
| Unique side effects associated with bortezomib- and IMiD-based regimens | 4 3 2 1 | 4 3 2 1 |
| Use of low-dose versus high-dose dexamethasone with lenalidomide | 4 3 2 1 | 4 3 2 1 |
| Emerging investigational compounds in the treatment of multiple myeloma | 4 3 2 1 | 4 3 2 1 |

**Was the activity evidence based, fair, balanced and free from commercial bias?**

☐ Yes ☐ No

If no, please explain: . . . . . .

**Will this activity help you improve patient care?**

☐ Yes ☐ No ☐ Not applicable

**Did the activity meet your educational needs and expectations?**

☐ Yes ☐ No

If no, please explain: . . . . . .

If no, please explain: . . . . . .

**Please respond to the following learning objectives (LOs) by circling the appropriate selection:**

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

**As a result of this activity, I will be able to:**

- Effectively apply the results of pivotal clinical research to the clinical management of newly diagnosed and relapsed MM. . . . . 4 3 2 1 N/M N/A
- 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. . . . . 4 3 2 1 N/M N/A
- Use biomarkers to assess risk for patients with MM, and recommend systemic treatment commensurate with prognosis and likelihood of therapeutic response. . . . . 4 3 2 1 N/M N/A
- Recognize treatment-associated side effects, and offer patients prophylactic or acute supportive management strategies to address them. . . . . 4 3 2 1 N/M N/A
- Differentiate emerging investigational compounds from existing agents used in the treatment of MM. . . . . 4 3 2 1 N/M N/A
- Identify current approaches to stem cell transplant for eligible patients with symptomatic MM, and recommend evidence-based induction regimens to facilitate long-term outcomes. . . . . 4 3 2 1 N/M N/A
- Recall the design and eligibility criteria for ongoing clinical trials in newly diagnosed and relapsed MM, and enroll or refer appropriate patients for study participation. . . . . 4 3 2 1 N/M N/A

**What other practice changes will you make or consider making as a result of this activity?**

. . . . . .

**What additional information or training do you need on the activity topics or other oncology-related topics?**

. . . . . .

**Additional comments about this activity:**

. . . . . .

**As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.**

☐ Yes, I am willing to participate in a follow-up survey. ☐ No, I am not willing to participate in a follow-up survey.

**REQUEST FOR CREDIT — Please print clearly**

Name: . . . . . Specialty: . . . . . .

Professional Designation:

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Telephone: . . . . . Fax: . . . . . .

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**Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.**

**I certify my actual time spent to complete this educational activity to be _____ hour(s).**

Signature: . . . . . Date: . . . . . .

**To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.**

YIRMM10

# Year in Review

## Multiple Myeloma: 2009-2010


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Hematologic Oncology™
UPDATE


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