Year in Review

Year in Review

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

Multiple Myeloma: 2010-2011

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Monograph
CD with PowerPoint slide kit including expert commentary

Multiple Myeloma: 2010-2011

2011 • Vol 1 • Issue 1

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CME Certified

Year in Review — Multiple Myeloma 2010-2011 Continuing Medical Education (CME) Information

OVERVIEW OF ACTIVITY

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 10% of all hematologic cancers and carries with it the worst death to new cases ratio (3:4) among the whole of the subtypes. The American Cancer Society estimated that 20,520 new MM cases will occur in the United States in 2011, with an estimated 10,610 deaths. The treatment of MM has improved dramatically over 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 uses 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

- Appraise recent data on therapeutic advances and changing practice standards in MM, and integrate this information into the selection of optimal systemic therapy for patients with MM.
- Compare and contrast the benefits and risks of lenalidomide- and bortezomib-based induction therapy, and consider the role of combined immunomodulatory/proteasome inhibitor regimens.
- Utilize biomarkers to risk-stratify patients with MM, and recommend systemic treatment commensurate with prognosis and likelihood of therapeutic response.
- Recognize the treatment-associated side effects of bortezomib, and offer patients acceptable alternative dosing/administration and/or supportive management interventions to address them.
- Communicate the benefits and risks of postinduction maintenance therapy to appropriately selected patients with MM.
- Consider recent Phase III trial data on the use of bisphosphonates for osteolytic and nonosteolytic MM when selecting frequency of administration and total duration of bisphosphonate therapy.
- 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

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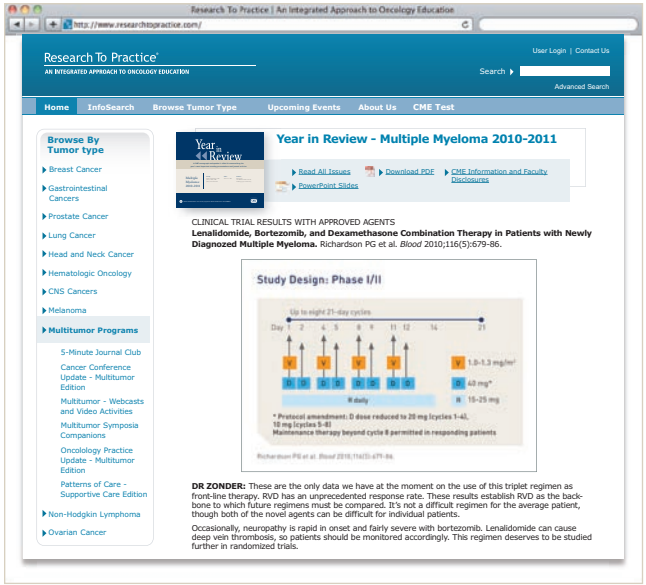

Visit ResearchToPractice.com/YIRMM11 Today!

The online version of *Year in Review — Multiple Myeloma* 2010-2011 includes:

- Interactive slide modules with faculty commentary reviewing the 22 primary papers and presentations featured in the monograph
- An annotated bibliography listing all secondary papers and presentations
- References with active web links for all papers and presentations taking users to actual abstracts and full-text publications
- Downloadable PowerPoint slides for each of the primary publications
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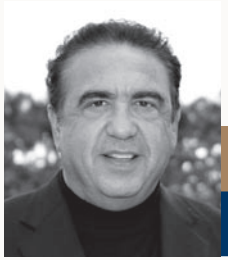

NEIL LOVE, MD

BACK WHERE IT ALL BEGAN

In early 2008, after the unprecedented data explosion at the 2007 American Society of Hematology (ASH) Annual Meeting where no fewer than 6 Phase III randomized trials in multiple myeloma were presented, our CME group sensed a great need for education in this challenging and unique disease. Within weeks we were swimming in previously uncharted waters as we attempted to conceptualize an educational resource that would expose practicing clinicians to these and other newly emerging trial results while also helping them to understand how this information should be applied to clinical practice. The result of this extensive investment of time and brainpower was not only our first major foray into multiple myeloma but also the creation of an entirely new educational format — *Year in Review*.

Since that time, 3 things have happened:

1. We have moved forward full force with myeloma education and have provided clinicians with an array of relevant perspectives on the disease.
2. We have successfully expanded *Year in Review* and have now produced similar editions focused on breast cancer, lung cancer, gastrointestinal cancer and non-Hodgkin lymphoma.
3. Multiple myeloma research has continued to outpace efforts in many other solid tumors and hematologic cancer.

To that end, we once again felt the need to "evaluate, distill and deliver," and as such we asked 3 clinical investigators and 10 oncologists in community-based practice to sift through the new mountain of information in multiple myeloma to determine what is most relevant to daily patient care. The 22 papers featured as "Primary" publications in this monograph/slide set are considered by our reviewers to be required reading for any physician providing care for patients with this disease. These are accompanied by brief comments from our faculty co-editors and 15 additional "Secondary" papers that are highlighted and annotated.

For us, this super-practical resource summarizes the latest chapter of progress that has been made in the field. But if history serves correctly, it is also another reminder that we are in the midst of a continually evolving story that gets better and more exciting each and every year.

— Neil Love, MD
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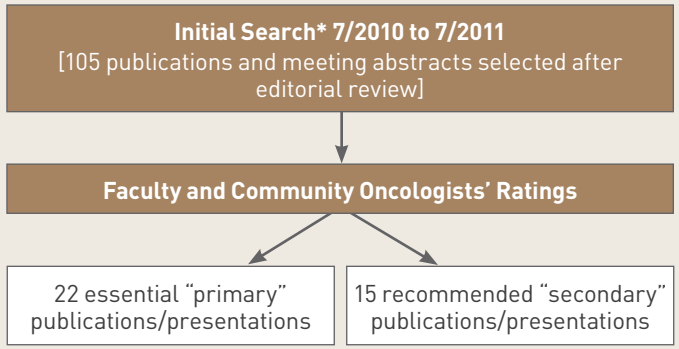
October 21, 2011

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



* PubMed July 22, 2010 through July 22, 2011. English language, clinical trials, controlled clinical trials, meta-analyses, practice guidelines, core clinical journals. Search of meeting abstracts from 2010 ASH, 2011 ASCO and International Myeloma Workshop 2011 annual meetings.

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CLINICAL TRIAL RESULTS WITH APPROVED AGENTS

8 Richardson PG et al. **Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.** *Blood* 2010;116(5):679-86.

10 McCarthy P et al. **Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB ECOG BMT-CTN 100104.** *Proc International Myeloma Workshop* 2011.

12 Attal M et al. **Maintenance treatment with lenalidomide after transplantation for myeloma: Analysis of secondary malignancies within the IFM 2005-02 trial.** *Proc International Myeloma Workshop* 2011.

14 Dimopoulos MA et al. **Lenalidomide and dexamethasone (LEN plus DEX) treatment in relapsed/refractory multiple myeloma (RRMM) patients (pts) and risk of second primary malignancies (SPM): Analysis of MM-009/010.** *Proc ASCO* 2011;Abstract 8009.

16 Bringhen S et al. **Efficacy and safety of once-weekly bortezomib in multiple myeloma patients.** *Blood* 2010;116(23):4745-53.

18 Moreau P et al. **Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomised, phase 3, non-inferiority study.** *Lancet Oncol* 2011;12(5):431-40.

20 Palumbo A et al. **A phase 3 study evaluating the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients ≥ 65 years with newly diagnosed multiple myeloma (NDMM): Continuous use of lenalidomide vs fixed-duration regimens.** *Proc ASH* 2010;Abstract 622.

22 Goldschmidt H et al. **Bortezomib-based induction therapy followed by autologous stem cell transplantation and maintenance therapy with bortezomib improves outcome in myeloma patients with gain 1q21 and t(4;14) — A subgroup analysis of the HOVON-65/GMMG-HD4 trial.** *Proc ASH* 2010;Abstract 305.

24 Cavo M et al; GIMEMA Italian Myeloma Network. **Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomised phase 3 study.** *Lancet* 2010;376(9758):2075-85.

26 Cavallo F et al. **Stem cell mobilization in patients with newly diagnosed multiple myeloma after lenalidomide induction therapy.** *Leukemia* 2011;25(10):1627-31.

28 Mateos MV et al. **Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial.** *Lancet Oncol* 2010;11(10):934-41.

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

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

34 Dimopoulos M et al. **The efficacy and safety of lenalidomide plus dexamethasone in relapsed and/or refractory multiple myeloma patients with impaired renal function.** *Cancer* 2010;116(16):3807-14.

MULTIPLE MYELOMA WORKUP AND RISK STRATIFICATION

36 Dimopoulos M et al; International Myeloma Workshop Consensus Panel 3. **Consensus recommendations for standard investigative workup: Report of the International Myeloma Workshop Consensus Panel 3.** *Blood* 2011;117(18):4701-5.

38 Munshi NC et al; International Myeloma Workshop Consensus Panel 2. **Consensus recommendations for risk stratification in multiple myeloma: Report of the International Myeloma Workshop Consensus Panel 2.** *Blood* 2011;117(18):4696-700.

NOVEL AGENTS UNDER INVESTIGATION

40 Leleu X et al. **Phase 2 study of 2 modalities of pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. IFM 2009-02.** *Proc ASH* 2010;Abstract 859.

42 Lacy MQ et al. **Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of two dosing strategies in dual-refractory disease.** *Blood* 2011;118(11):2970-5.

44 Jakubowiak AJ et al. **Carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma: Initial results of phase I/II MMRC trial.** *Proc ASH* 2010;Abstract 862.

BONE-TARGETED TREATMENT

46 Morgan GJ et al; National Cancer Research Institute Haematological Oncology Clinical Study Group. **First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): A randomised controlled trial.** *Lancet* 2010;376(9757):1989-99.

48 Boyd K et al. **Does zoledronic acid (ZOL) reduce skeletal-related events (SREs) and improve progression-free survival (PFS) in patients (pts) with multiple myeloma (MM) with or without bone disease? MRC Myeloma IX study results.** *Proc ASCO* 2011;Abstract 8010.

48 Davies FE et al. **Bisphosphonate treatment in multiple myeloma: Should they be used until progression?** *Proc ASCO* 2011;Abstract 8011.

SECONDARY PUBLICATIONS/PRESENTATIONS (RECOMMENDED)

CLINICAL TRIAL RESULTS WITH APPROVED AGENTS

1. Palumbo A et al. **Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) in newly diagnosed multiple myeloma (MM) patients: A phase III study.** *Proc EHA 16th Congress* 2011.

   The first reported study evaluating the role of ASCT versus induction therapy in the era of novel agents. A statistically significant PFS benefit was reported in patients with newly diagnosed multiple myeloma (NDMM) receiving MEL200 compared to MPR (18-month PFS: 78% versus 68%), although toxicities were significantly higher. No significant difference in OS was reported in the current analysis.

2. Harousseau JL et al. **Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: Results of the IFM 2005-01 phase III trial.** *J Clin Oncol* 2010;28(30):4621-9.

   VD significantly improved postinduction and post-transplantation CR, near CR and ≥VGPR rates compared to VAD and resulted in a trend for longer PFS in patients with NDMM.

3. Gay F et al. **Clarithromycin (Biaxin)-lenalidomide-low-dose dexamethasone (BiRd) versus lenalidomide-low-dose dexamethasone (Rd) for newly diagnosed myeloma.** *Am J Hematol* 2010;85(9):664-9.

   In a retrospective analysis of 72 patients with NDMM, addition of clarithromycin to Rd appeared to significantly improve CR, time to disease progression and PFS outcomes.

4. Roussel M et al. **Frontline therapy with bortezomib, lenalidomide, and dexamethasone (VRD) induction followed by autologous stem cell transplantation, VRD consolidation and lenalidomide maintenance in newly diagnosed multiple myeloma patients: Primary results of the IFM 2008 phase II study.** *Proc ASH* 2010;Abstract 624.

   VRD induction followed by ASCT and VRD consolidation produced high-quality responses and was well tolerated in patients with NDMM younger than age 65. ORR after ASCT was 94% (including 32% VGPR, 13% CR and 23% stringent CR).

5. Cavo M et al. **Bortezomib-based induction treatments improve outcomes of newly diagnosed multiple myeloma patients with high-risk cytogenetic abnormalities.** *Proc ASH* 2010;Abstract 781.

   In patients with NDMM receiving bortezomib-based induction treatments, del(13q) alone and del(17p) alone did not adversely influence PFS and OS. Presence of t(4;14) alone did not adversely influence PFS but was associated with a shorter OS. Presence of both del(17p) and t(4;14) was likely to confer a dismal clinical outlook.

6. Harousseau JL et al. **Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: Analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone.** *Blood* 2010;116(19):3743-50.

   An analysis of the prognostic effect of response on time-to-event parameters in the VISTA trial concluded that CR is an important treatment goal and supported prolonged VMP therapy to achieve maximal response.

7. Zonder JA et al. **Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: A randomized Southwest Oncology Group trial (S0232).** *Blood* 2010;116(26):5838-41.

   One-year PFS, ORR and VGPR were superior with RD versus dexamethasone, whereas 1-year OS was similar. Toxicities were more pronounced with RD, including Grade 3 neutropenia and thromboembolic events despite aspirin prophylaxis.

8 Kumar S et al. **Novel three- and four-drug combination regimens of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for previously untreated multiple myeloma: Results from the multi-center, randomized, phase 2 EVOLUTION study.** *Proc ASH* 2010;Abstract 621.

Continuous weekly C in the VDC regimen was associated with high response rates and rapid responses versus VDR and VDCR. VDCR did not result in a substantial increase in response rate and was associated with a modest increase in the incidence of hematologic toxicities.

9 Benevolo G et al. **The efficacy and safety of bortezomib and dexamethasone as a maintenance therapy in patients with advanced multiple myeloma who are responsive to salvage bortezomib-containing regimens.** *Cancer* 2011;117(9):1884-90.

Bortezomib and dexamethasone was effective (1-year ORR: 76%) and well tolerated as maintenance therapy in 49 patients with MM who were responsive to prior bortezomib-based salvage regimens.

10 Palumbo AP et al. **Incidence of second primary malignancy (SPM) in melphalan-prednisone-lenalidomide combination followed by lenalidomide maintenance (MPR-R) in newly diagnosed multiple myeloma patients (pts) age 65 or older.** *Proc ASCO* 2011;Abstract 8007.

Among patients with NDMM, an imbalance of AML incidence was observed in patients who received MPR/MPR-R versus MP, but incidence was low (0.7% versus 0%), and SPM risk was similar in other studies.

11 Rossi AC et al. **Incidence of second primary malignancies (SPM) after 6-years follow-up of continuous lenalidomide in first-line treatment of multiple myeloma (MM).** *Proc ASCO* 2011;Abstract 8008.

No cases of secondary MDS/AML occurred among 68 patients with NDMM who received BiRD after 4 years.

12 Madan S et al. **Efficacy of retreatment with immunomodulatory drugs (IMiDs) in patients receiving IMiDs for initial therapy of newly diagnosed multiple myeloma.** *Blood* 2011;118(7):1763-5.

The efficacy of re-treatment on relapse with lenalidomide was higher than re-treatment with thalidomide among 113 evaluable patients.

NOVEL AGENTS UNDER INVESTIGATION

13 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* 2010;Abstract 864.

Single-agent pomalidomide achieved clinically significant durable responses with a manageable safety profile in patients with heavily pretreated relapsed or refractory MM. Addition of dexamethasone can reinduce response in selected patients.

14 Siegel DS et al; Multiple Myeloma Research Consortium (MMRC). **PX-171-003-A1, an open-label, single-arm, phase (Ph) II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (R/R MM): Long-term follow-up and subgroup analysis.** *Proc ASCO* 2011;Abstract 8027.

In 257 response-evaluable patients with relapsed or refractory MM, single-agent carfilzomib resulted in an ORR of 24% and a median duration of response of 7.4 months. No new, unexpected or cumulative toxicities were observed, and adverse events were clinically manageable.

BONE-TARGETED TREATMENT

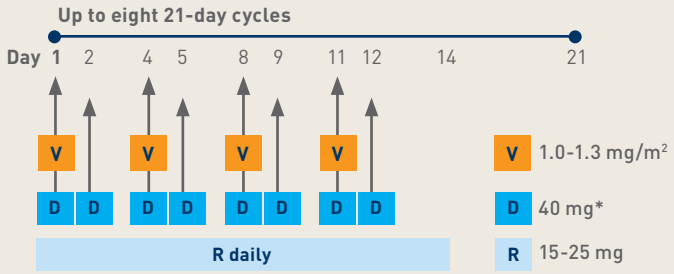
15 Henry DH et al. **Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.** *J Clin Oncol* 2011;29(9):1125-32.

Denosumab was noninferior (trending to superiority) to zoledronic acid in preventing or delaying first on-study SRE. ONJ occurred at similar low rates in both treatment groups.

Lenalidomide, Bortezomib, and Dexamethasone Combination Therapy in Patients with Newly Diagnosed Multiple Myeloma

Richardson PG et al.
Blood 2010;116(5):679-86.

Study Design: Phase I/II



* Protocol amendment: D dose reduced to 20 mg (cycles 1-4), 10 mg (cycles 5-8)
Maintenance therapy beyond cycle 8 permitted in responding patients

Richardson PG et al. *Blood* 2010;116(5):679-86.

Introduction

- Bortezomib (V) is approved for the treatment of multiple myeloma (MM).
- Lenalidomide (R) in combination with dexamethasone (D) is approved for the treatment of relapsed MM after ≥1 prior therapy.
- RV ± D is active and well tolerated in relapsed/refractory MM.
- RD and VD are active in front-line MM.
- Current study goals: To determine the maximum tolerated dose of RVD and to assess safety and efficacy in patients with previously untreated MM.

Richardson PG et al. *Blood* 2010;116(5):679-86.

Baseline Characteristics

Characteristic	All patients (n = 66)
Median age	58 years
Male	55%
Myeloma type	
IgG	68%
IgA	23%
Light chain	9%
ISS Stage II/III at diagnosis	56%

Richardson PG et al. *Blood* 2010;116(5):679-86.

Best Response to Treatment

Response	All patients (n = 66)	Phase II population (n = 35)
Complete response (CR)	29%	37%
Near CR (nCR)	11%	20%
Very good partial response (VGPR)	27%	17%
Partial response (PR)	33%	26%
CR + nCR	39%	57%
CR + nCR + VGPR	67%	74%
At least PR	100%	100%

Per EBMT criteria, all response categories, including VGPR, required a confirmatory assessment at 6 weeks.

Richardson PG et al. *Blood* 2010;116(5):679-86.

Author Conclusions

- RVD is a highly effective regimen for previously untreated MM.
  - May represent the basis of future standard treatment in this setting.
- Phase III studies are evaluating VD with or without R (NCT00522392) and RD with or without V (NCT00644228) to assess the benefit of the 3-drug approach.
- An international prospective study is ongoing to assess this combination with or without autologous stem cell transplant, followed by maintenance.

Richardson PG et al. *Blood* 2010;116(5):679-86.

Select Adverse Events

Nonhematologic	All grades	Grade 3 or 4
Sensory neuropathy	80%	2%
Fatigue	64%	3%
Neuropathic pain	32%	3%
Hematologic		
Lymphopenia	14%	14%
Thrombocytopenia	NR	6%
Neutropenia	NR	9%
Thrombosis	6%	5%

NR = not reported

Richardson PG et al. *Blood* 2010;116(5):679-86.

Faculty Comments

DR ZONDER: These are the only data we have at the moment on the use of this triplet regimen as front-line therapy. RVD has an unprecedented response rate. These results establish RVD as the backbone to which future regimens must be compared. It's not a difficult regimen for the average patient, though both of the novel agents can be difficult for individual patients. Occasionally, neuropathy is rapid in onset and fairly severe with bortezomib. Lenalidomide can cause deep vein thrombosis, so patients should be monitored accordingly. This regimen deserves to be studied further in randomized trials.

Phase III Intergroup Study of Lenalidomide versus Placebo Maintenance Therapy Following Single Autologous Stem Cell Transplant (ASCT) for Multiple Myeloma (MM): CALGB ECOG BMT-CTN 100104

McCarthy P et al.
Proc International Myeloma Workshop 2011.

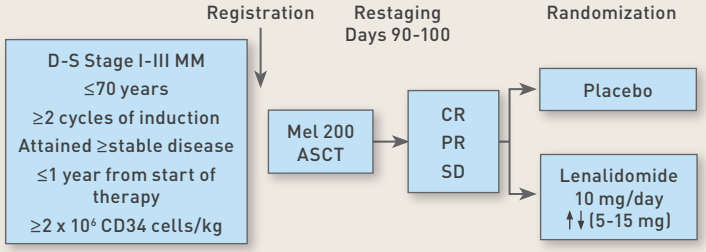
Efficacy

	Placebo (n = 229)	Lenalidomide (n = 231)	Hazard ratio	*p*-value
Median TTP	30.9 mo	48.0 mo	0.44	<0.0001
OS (events)	39 deaths	23 deaths	0.51	0.018
Median event-free survival (EFS)	30.9 mo	43.4 mo	0.51	<0.0001

Median follow-up from transplant: 28 months

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

CALGB-100104 Study Schema



Primary objective: Determine the efficacy of lenalidomide in prolonging time to progression (TTP)
Secondary objectives: CR rate post-ASCT, overall survival (OS), feasibility of long-term lenalidomide administration

CR = complete response; PR = partial response; SD = stable disease

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Second Cancers: Hematologic

	Placebo (n = 229)	Lenalidomide (n = 231)
Hematologic cancers	0	8
Myelodysplastic syndromes	0	1
Acute myeloid leukemia	0	5
Acute lymphoblastic leukemia	0	1
Hodgkin lymphoma	0	1

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Second Cancers: Solid Tumors

	Placebo (n = 229)	Lenalidomide (n = 231)
Gastrointestinal cancer	0	2
Breast cancer	0	2
Gynecologic cancer	0	2
CNS cancer	0	1
Prostate cancer	0	1
Thyroid cancer	0	1
Melanoma	2	1
Carcinoid tumor	1	0
Sarcoma	1	0

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Author Conclusions (continued)

> Lenalidomide prolonged TTP and EFS even after stratification by diagnostic ß2M level and prior thalidomide or lenalidomide induction therapy (data not shown).

> TTP and EFS were superior in patients receiving lenalidomide as part of induction and post-ASCT maintenance or continued therapy.

> After primary therapy, maintenance or continued therapy studies with lenalidomide and other agents, alone or in combination, may determine optimal strategies for long-term MM disease control.

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Author Conclusions

> Maintenance therapy with lenalidomide after single ASCT significantly prolongs TTP versus placebo.

> A statistically significant improvement in OS was seen on the lenalidomide arm of the most recent data analysis (median follow-up of 28 months post-ASCT).

> Second cancers may be increased in patients receiving lenalidomide but without significant effect on EFS or OS (at current analysis).

> Research efforts continue to identify risk factors for the development of second cancers.

McCarthy P et al. *Proc International Myeloma Workshop* 2011.

Faculty Comments

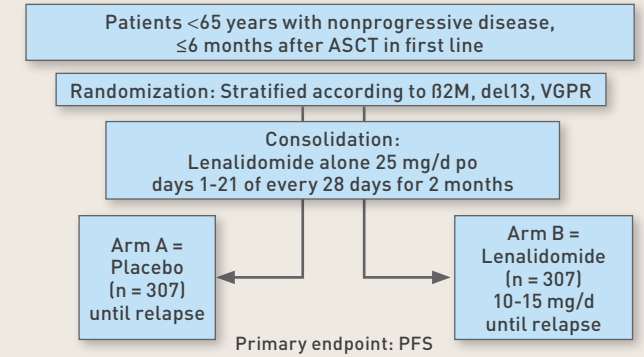
DR BENSINGER: This trial reported a similar higher incidence of second primary cancers to that seen on the French IFM 2005-02 trial. What's different and interesting is that the CALGB study reported a 50% reduction in time to disease progression for patients who received lenalidomide maintenance versus placebo. A statistically significant overall survival benefit was also reported.

This is a potential "game changer" even if more second primary cancers occur with lenalidomide maintenance. If you can show an improvement in survival, then it negates the concern about second primary cancers because there were so few. Still, I don't believe the verdict is in and will await further follow-up on these 2 studies.

Maintenance Treatment with Lenalidomide After Transplantation for Myeloma: Analysis of Secondary Malignancies Within the IFM 2005-02 Trial

Attal M et al.
Proc International Myeloma Workshop 2011.

IFM 2005-02 Study Schema



Attal M et al. *Proc International Myeloma Workshop* 2011.

Introduction

> The Phase III IFM 2005-02 trial evaluated the efficacy of lenalidomide maintenance after transplantation for patients with multiple myeloma.
  – Maintenance lenalidomide improved progression-free survival (PFS) and was well tolerated.
  – However, several patients developed secondary hematologic or solid cancers.
> Analyses of secondary cancers reported by all IFM centers for patients on IFM 2005-02 were conducted.

Attal M et al. *Proc International Myeloma Workshop* 2011.

Progression-Free and Overall Survival

	Placebo (n = 307)	Lenalidomide (n = 307)	Hazard ratio	*p*-value
PFS* (months)	24	41	0.5	$<10^{-8}$
5-year OS	73%	79%	1.05	Not significant

* PFS benefit was observed across all stratified patient subgroups.
Median follow-up: 36 months postrandomization, 46 months postdiagnosis
PFS = progression-free survival; OS = overall survival

Attal M et al. *Proc International Myeloma Workshop* 2011.

Second Primary Cancers

	Placebo (n = 302)	Lenalidomide (n = 306)
Hematologic cancers	3	11
AML/MDS	3	5
ALL	0	2
Hodgkin lymphoma	0	4
Solid tumors	3	12

AML = acute myeloid leukemia; MDS = myelodysplastic syndromes; ALL = acute lymphoblastic leukemia

Attal M et al. *Proc International Myeloma Workshop* 2011.

Author Conclusions (continued)

> Other risk factors for secondary cancers were:
- Age >55 years
- Male sex
- International Staging System Stage III
- Induction with dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) (data not shown)

> Longer follow-up is needed to determine the effect on OS

Attal M et al. *Proc International Myeloma Workshop* 2011.

Author Conclusions

> Maintenance therapy with lenalidomide:
- Is associated with a low rate of neuropathy and DVT (data not shown)
- Results in improved PFS compared to placebo: 50% reduction in the risk of disease progression in all stratified subgroups, including response, β2M and FISH
- Is associated with increased risk of secondary cancers, primarily after 24 months

Attal M et al. *Proc International Myeloma Workshop* 2011.

Faculty Comments

DR BENSINGER: This trial demonstrated markedly improved progression-free survival for the patients who received lenalidomide. The higher incidence of second cancers is somewhat concerning. These tended to be hematologic cancers, not largely seen in the group who received placebo, so these results raised the issue of prior melphalan exposure and possible second cancers.

DR ZONDER: I believe the increased risk of secondary cancers observed with lenalidomide is outweighed by the antimyeloma benefit that is obtained. The emerging story from the maintenance trials is that longer therapy results in longer disease control. We've known that a risk of secondary cancers exists after anthracycline-containing and alkylator-containing therapy.

Lenalidomide and Dexamethasone (LEN plus DEX) Treatment in Relapsed/Refractory Multiple Myeloma Patients (Pts) and Risk of Secondary Primary Malignancies (SPM): Analysis of MM-009/010

Dimopoulos MA et al.
Proc ASCO 2011;Abstract 8009.

SPM Incidence Rates — Active Treatment Phase (Safety Population)

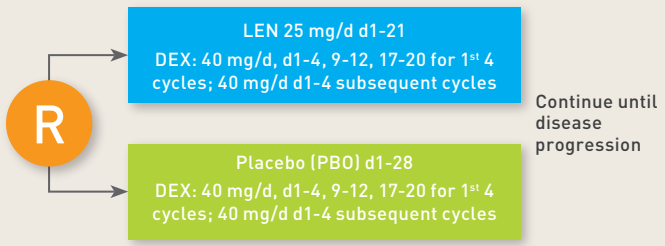
Invasive SPM	Incidence*	
	LEN + DEX (n = 353)	PBO + DEX (n = 350)
Hematologic AML/MDS B-cell malignancies	0.42 0.42 0	0 0 0
Solid tumors	1.28	0.91
Noninvasive SPM		
Nonmelanoma skin cancer	2.40	0.91
Total SPM	3.98	1.38

* Incidence rate (IR) reported per 100 person-years (PY)

Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

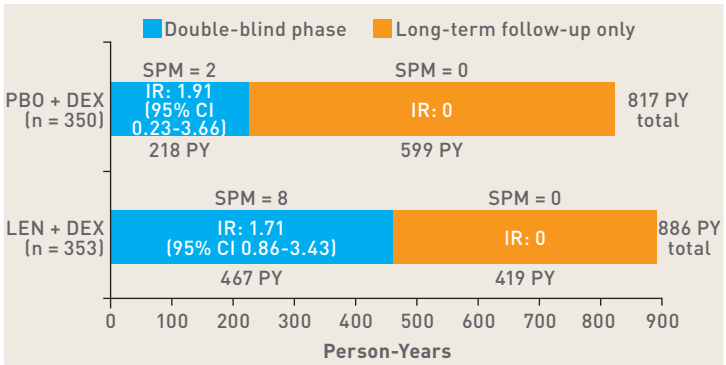
MM-009/010 Phase III Trial Schemas

Analysis of pooled data from patients with relapsed/refractory multiple myeloma (RRMM) treated in 2 Phase III studies (MM-009 and MM-010)



Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

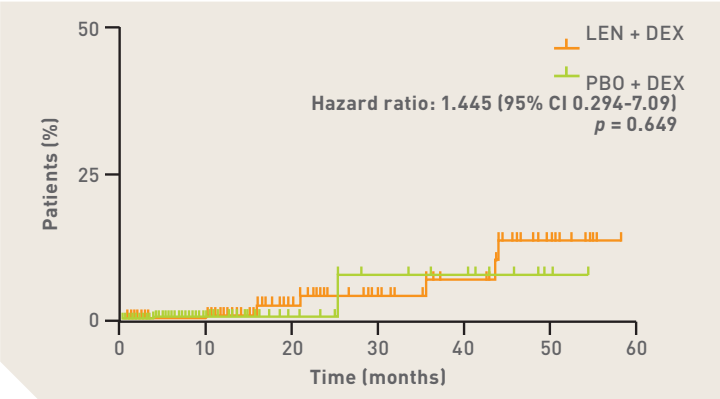
Invasive SPM Incidence Rates — Treatment and Follow-Up



Includes MDS and breast carcinoma in situ but not nonmelanoma skin cancers

With permission from Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

Time to Invasive SPM — Treatment Period



With permission from Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

Author Conclusions

> No difference in incidence rates of invasive SPMs in LEN + DEX arm versus PBO + DEX arm in MM-009/010

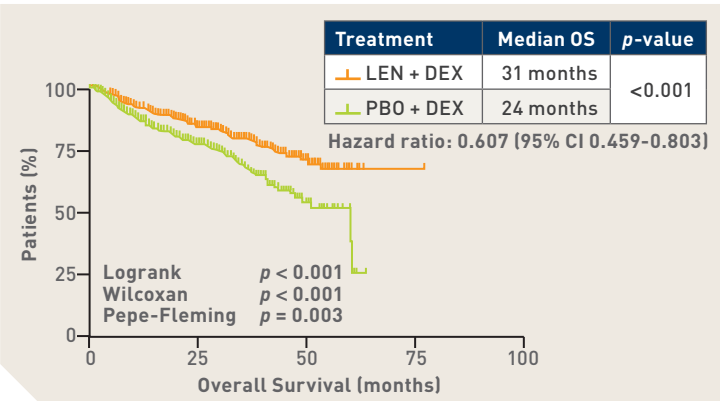
> SPM incidence rates were low and similar to the background incidence among persons similarly aged in the general population

> Overall survival was significantly longer for patients who received LEN + DEX
  – Confirmed with long-term follow-up despite ~50% of patients in the PBO + DEX arm crossing over to receive LEN-based therapy

> The overall benefit-risk profile of LEN in RRMM remains strongly positive

Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

LEN + DEX Overall Survival (OS) (Up to Unblinding)



With permission from Dimopoulos MA et al. *Proc ASCO* 2011;Abstract 8009.

Faculty Comments

DR BENSINGER: A signal of increased second primary cancer has been seen with lenalidomide in some of the maintenance trials. This retrospective pooled analysis found that no statistically significant difference was observed in the numbers of second primary tumors in patients with relapsed/refractory myeloma who received lenalidomide/dexamethasone versus those who received dexamethasone and placebo. This adds assurance to the idea that lenalidomide by itself may not increase the incidence of second primary cancer. An issue I would have liked to have seen addressed is whether prior melphalan exposure has any effect on the incidence of second primary cancer. In discussions of maintenance therapy, prior melphalan exposure is brought up as having a possible interaction.

Efficacy and Safety of Once-Weekly Bortezomib in Multiple Myeloma Patients

Bringhen S et al.
Blood 2010;116(23):4745-53.

Introduction

> The Phase III GIMEMA trial comparing VMPT-VT to VMP for elderly patients with newly diagnosed myeloma reported VMPT-VT was superior in response rate (complete response rate: 38% versus 24%) and progression-free survival (56% versus 41%) (*J Clin Oncol* 2010;28:5101-9).
> Although patients on both arms initially received twice-weekly bortezomib, the protocol was amended to evaluate whether once-weekly bortezomib could decrease toxicity while maintaining efficacy.
> Current analysis objective: To assess the effect of bortezomib schedule change on clinical outcomes and safety, specifically on the incidence and reversibility of bortezomib-induced peripheral neuropathy (PN), for patients enrolled in GIMEMA.

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Survival and Best Response Rates

	Once-weekly bortezomib (n = 369)	Twice-weekly bortezomib (n = 134)	*p*-value
3-year progression-free survival	50%	47%	1.0
3-year overall survival	88%	89%	0.54
Overall response rate	85%	86%	0.78
Complete response	30%	35%	0.27
Very good partial response	25%	19%	0.15
Partial response	30%	32%	0.66
Stable disease	13%	9%	0.27

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Bortezomib Treatment Exposure and Select Grade 3 or 4 Adverse Events (AEs)

	Once weekly (n = 369)	Twice weekly (n = 134)	*p*-value
Cumulative planned dose	46.8 mg/m^2	67.6 mg/m^2	—
Median cumulative dose delivered	39.4 mg/m^2	40.1 mg/m^2	0.65
Planned dose delivered	84%	59%	—
Patients who received ≥90% of planned dose	39%	13%	<0.001
Nonhematologic AE Neuropathy Sensory neuropathy	35% 8% 3%	51% 28% 16%	0.003 <0.001 <0.001
Dermatologic events	2%	7%	0.006

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Features of Peripheral Neuropathy

	Once weekly	Twice weekly	*p*-value
Cumulative proportion of patients with PN at 18 months			
Any grade Sensory neuropathy	40% 27%	72% 46%	<0.001 <0.001
Grade 3 or 4 Sensory neuropathy	9% 4%	36% 21%	<0.001 <0.001
Bortezomib dose modification caused by PN			
Dose reduction	17%	41%	<0.001
Dose discontinuation	5%	15%	<0.001
Median time to dose reduction	3.8 mo	2.8 mo	0.08

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Author Conclusions

> Once-weekly infusion of bortezomib in combination with MPT is a valuable treatment schedule for elderly patients with newly diagnosed disease.

> Initial twice-weekly bortezomib followed by a rapid reduction to a once-weekly schedule may be suggested in selected patients with clinically aggressive disease (ie, those with incipient renal failure or extensive pain) (data not shown).

> The once-weekly schedule significantly reduced the incidence of PN and decreased the rate of discontinuation compared to the twice-weekly schedule, resulting in similar cumulative bortezomib doses in the 2 groups.

> The improvement in the safety profile was not associated with any reduction in the efficacy of the regimen.

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Features of Peripheral Neuropathy (continued)

	Once weekly (n = 77)	Twice weekly (n = 73)	*p*-value
Outcome of Grade 2-4 PN			
Resolution	34%	40%	0.74
Improvement	30%	26%	—
Persistence	36%	34%	—
Median time to recovery	2.3 mo	3.2 mo	0.005

Bringhen S et al. *Blood* 2010;116(23):4745-53.

Faculty Comments

DR ZONDER: This analysis of the VMP versus VMPT-VT study published in *Blood* focuses on the incidences of peripheral neuropathy (PN) with weekly versus twice-weekly bortezomib administration on the trial. A large reduction was evident in the incidence of Grade 3 and 4 PN in addition to discontinuations related to PN.

Similar data exist from the Mayo Clinic on the use of once- versus twice-weekly bortezomib with similar results — less neuropathy, same efficacy. When I administer bortezomib with MP or with cyclophosphamide/dexamethasone, I use the once-weekly schedule.

Subcutaneous versus Intravenous Administration of Bortezomib in Patients with Relapsed Multiple Myeloma: A Randomised, Phase 3, Non-Inferiority Study

Moreau P et al.
Lancet Oncol 2011;12(5):431-40.

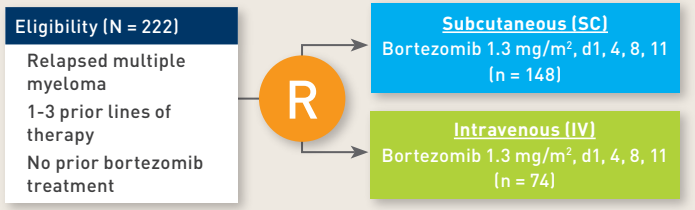
Treatment Exposure

	Bortezomib SC (n = 147)*	Bortezomib IV (n = 74)
Median number of cycles (range)	8 (1-10)	8 (1-10)
Median time on study	22.6 weeks	22.6 weeks
Median cumulative bortezomib dose	33.76 mg/m^2	31.46 mg/m^2
Patients receiving dexamethasone	82 (56%)	39 (53%)

*Three patients had protocol violations for route of administration.

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

Phase III Trial of Subcutaneous versus Intravenous Bortezomib Administration



Up to 8 treatment cycles (plus 2 cycles if SD or PR)

If <CR after 4 cycles, 20 mg dexamethasone on days 1, 2, 4, 5, 8, 9, 11, 12 added in the next 4 cycles

SD = stable disease; PR = partial response; CR = complete response

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

Primary Endpoint: Overall Response Rate After 4 Cycles

Clinical variable	Bortezomib SC (n = 145)*	Bortezomib IV (n = 73)*
Overall response rate†	42%	42%
Complete response	6%	8%
Partial response	36%	34%
Very good partial response	4%	3%

* Three patients in the SC group and 1 patient in the IV group were not evaluable for response.
†*p*-value of 0.002 meets prespecified criteria for fulfilling noninferiority hypothesis of SC versus IV bortezomib.

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

Additional Efficacy Outcomes

Responding patients (after 8 cycles)	Bortezomib SC (n = 76)	Bortezomib IV (n = 38)
Median time to first response	1.4 mo	1.4 mo
Median time to best response	1.6 mo	1.5 mo
Median duration of response	9.7 mo	8.7 mo
Intent-to-treat population	**(n = 148)**	**(n = 74)**
Median time to progression	10.4 mo	9.4 mo
Median progression-free survival	10.2 mo	8.0 mo
1-year overall survival rate	72.6%	76.7%

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

Author Conclusions

> SC bortezomib was noninferior in terms of efficacy compared to IV administration.

> The pharmacokinetic and pharmacodynamic profiles of SC and IV bortezomib are similar (data not shown).

> SC administration of bortezomib appears to have an improved safety profile compared to IV administration.

– Significantly lower rates of peripheral neuropathy of all grades were observed in patients administered SC bortezomib.

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

Select Grade ≥3 Adverse Events

Adverse event	Bortezomib SC (n = 147)	Bortezomib IV (n = 74)
Any treatment-related adverse event	39%	55%
Neutropenia	18%	18%
Thrombocytopenia	13%	19%
Anemia	12%	8%
Leukopenia	6%	7%
Peripheral sensory neuropathy	**5%**	**15%**

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

Faculty Comments

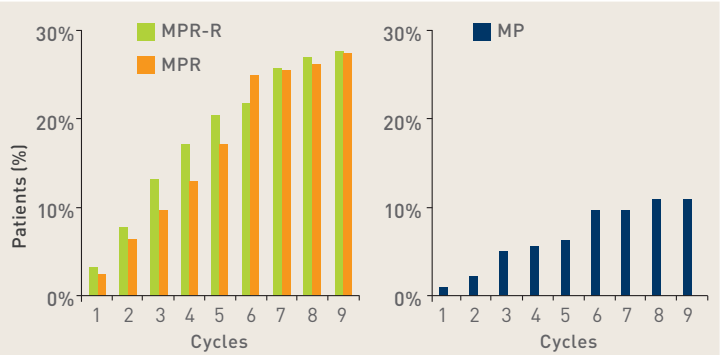
DR BENSINGER: This is a nice IFM trial in which patients with relapsed, bortezomib-naïve disease were randomly assigned to receive either subcutaneous (SC) or intravenous (IV) bortezomib. No major differences in the pharmacokinetics of SC versus IV administration were observed. Patient outcomes were also similar — response rates, time to progression and overall survival were identical.

The interesting finding of this study is that SC bortezomib caused less toxicity, specifically less neurotoxicity. A trend toward fewer cytopenias was also observed. The take-home message for me is that SC bortezomib is equally efficacious to IV, and it is associated with less neurotoxicity and is potentially more convenient. I have adopted SC bortezomib in my practice.

A Phase III Study Evaluating the Efficacy and Safety of Lenalidomide Combined with Melphalan and Prednisone in Patients ≥ 65 Years with Newly Diagnosed Multiple Myeloma (NDMM): Continuous Use of Lenalidomide vs Fixed-Duration Regimens

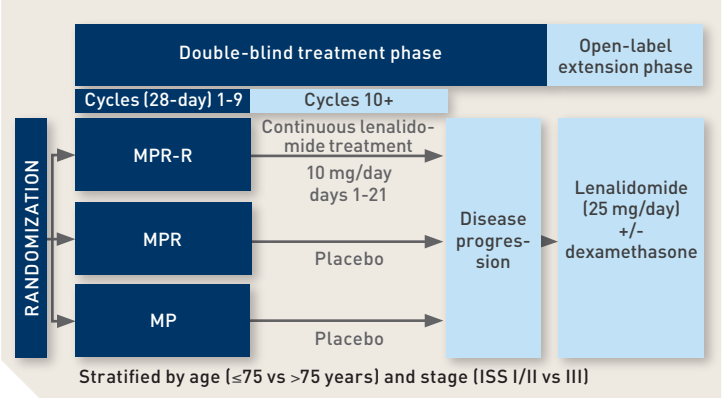
Palumbo A et al.
Proc ASH 2010;Abstract 622.

Response Rate



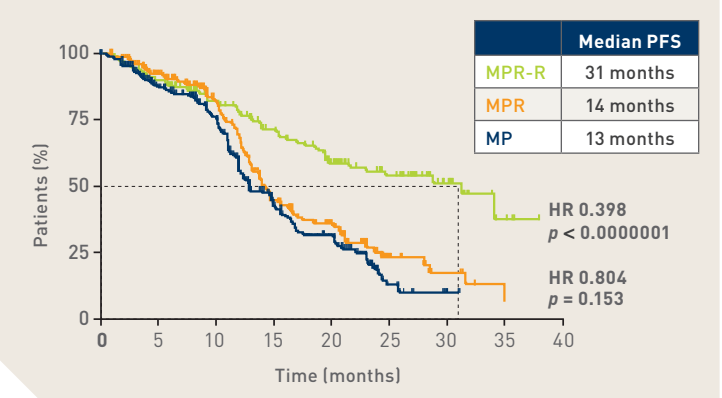
With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Study Design



Palumbo A et al. *Proc ASH* 2010;Abstract 622.

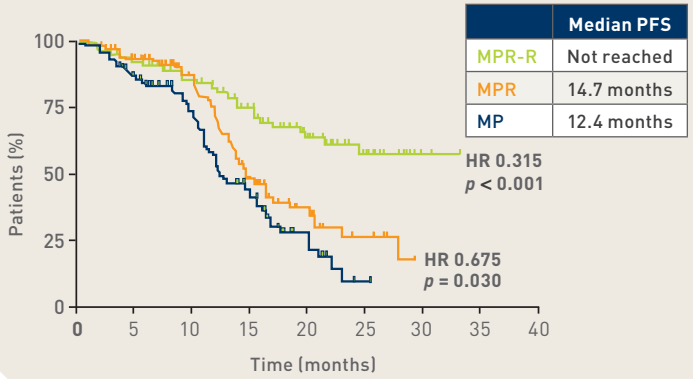
Progression-Free Survival (PFS) All Patients (25 Months Follow-Up)



	Median PFS
MPR-R	31 months
MPR	14 months
MP	13 months

With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Progression-Free Survival (PFS) Patients Age 65-75 Years



With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Author Conclusions

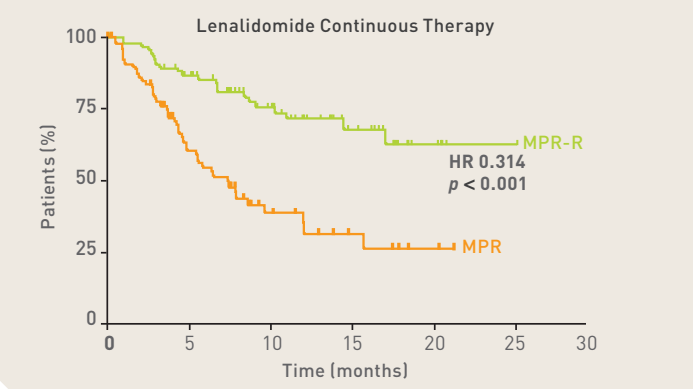
> Patients receiving MPR-R for NDMM achieved a higher overall response rate, as well as better-quality and more rapid responses versus MP.

> MPR-R compared to fixed-duration regimens of MP and MPR resulted in an unprecedented reduction in the risk of progression with a manageable safety profile and similar rates of progressive disease.
- Median PFS: 31 months ($p < 0.0000001$)
- Greatest benefit reported in patients age 65–75

> Continuous lenalidomide therapy with MPR-R may be superior to regimens of limited duration by providing sustained disease control in transplant-ineligible patients with NDMM.

Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Landmark Analysis — PFS



With permission from Palumbo A et al. *Proc ASH* 2010;Abstract 622.

Faculty Comments

DR ZONDER: This study compared MP to MP with lenalidomide (R) and MPR followed by R. These data indicate how important it is to continue lenalidomide therapy. One disappointing aspect about this study was that even though the overall response rates were similar between the 2 MPR arms, that did not translate into a clinically significant improvement in duration of response compared to MP alone. That surprises me.

If it turns out that an exponential increase of secondary cancer occurs beyond 2 or 3 years, then we'll certainly have to figure out what the optimal duration of therapy is, but right now it would seem that the optimal duration of lenalidomide therapy is until disease progression.

Bortezomib-Based Induction Therapy Followed by Autologous Stem Cell Transplantation and Maintenance Therapy with Bortezomib Improves Outcome in Myeloma Patients with Gain 1q21 and t(4;14) — A Subgroup Analysis of the HOVON-65/GMMG-HD4 Trial

Goldschmidt H et al.
Proc ASH 2010;Abstract 305.

Prognostic Effect of Chromosomal Abnormalities on Outcome

	PFS at 36 months			OS at 36 months		
	Present	Absent	*p*-value	Present	Absent	*p*-value
del(8p21)	34%	54%	0.005	67%	83%	NS
del(13q14)	39%	58%	0.010	73%	84%	0.006
del(17p13)	22%	51%	<0.001	36%	83%	<0.001
+1q21	22%	56%	0.002	71%	84%	0.010
t(4;14)	31%	51%	0.020	55%	83%	<0.001

PFS = progression-free survival; OS = overall survival; NS = not significant

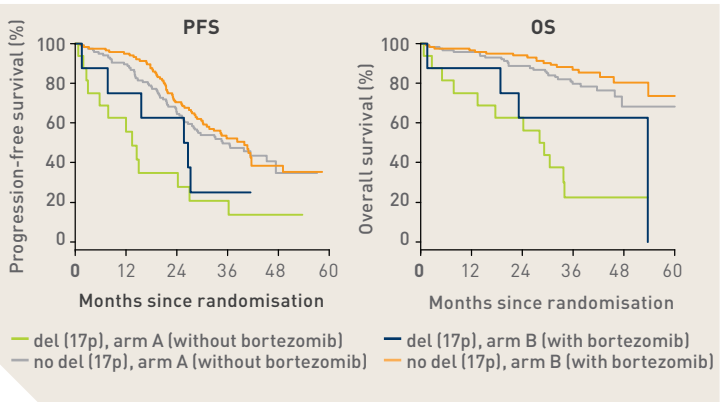
Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

HOVON-65/GMMG-HD4 Trial: Background and Methods

- Chromosomal aberrations are important prognostic parameters in multiple myeloma.
- This analysis evaluated the association of FISH results and outcome of a subgroup of patients within the HOVON-65/GMMG-HD4 trial.
- **Arm A (n = 131)**: Vincristine/doxorubicin/dexamethasone (VAD) x 3 with autologous stem cell transplant (ASCT) → thalidomide ≤2 years
- **Arm B (n = 127)**: Bortezomib/doxorubicin/dexamethasone (PAD) x 3 with ASCT → bortezomib ≤2 years
- All patients received: Hematopoietic stem cell mobilization with CAD and G-CSF and 1-2 cycles of high-dose melphalan with ASCT → maintenance therapy

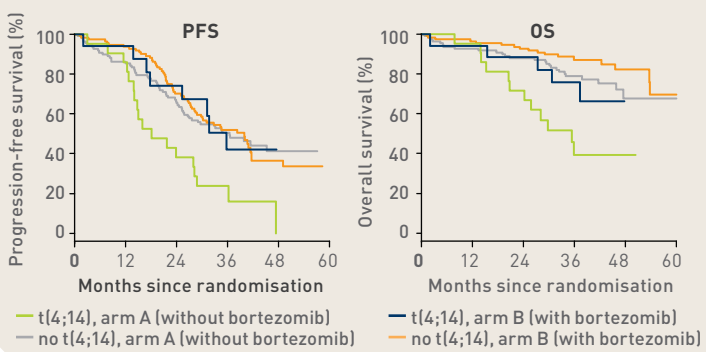
Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

Comparison between Both Study Arms Deletion 17p13



With permission from Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

Comparison between Both Study Arms Translocation t(4;14)



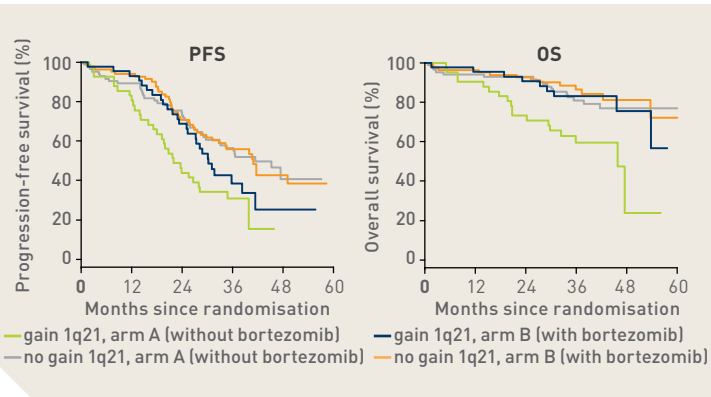
With permission from Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

Author Conclusions

> Chromosomal aberrations with prognostic effect on PFS and OS within the GMMG-HD4 trial were as follows:
> – del(13q), del(17p), t(4;14) and +1q
> Deletion of chromosome 13q as exclusive chromosomal aberration without the presence of del(17p) and t(4;14) indicates no effect on outcome.
> These data indicate that ASCT and maintenance therapy with bortezomib significantly improve outcome in patients with myeloma with gain 1q and t(4;14).
> In contrast, ASCT and maintenance therapy with bortezomib do not modify the outcome of patients with del(17p), for whom a standard therapy has yet to be identified.

Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

Comparison between Both Study Arms Gain 1q21



With permission from Goldschmidt H et al. *Proc ASH* 2010;Abstract 305.

Faculty Comments

DR WOLF: This report focuses on a subgroup analysis of the HOVON study and on the ability of bortezomib to overcome adverse prognostic features. Patients with t(4;14) who received VAD have poor prognoses, with a median progression-free survival time half as long as those without the translocation, yet no such negative effect was observed in patients on the PAD arm. PAD also resulted in improved 3-year overall survival for patients with t(4;14). If you compare VAD to PAD, an advantage was evident, but it was much smaller in those without the 4;14 translocation. The message here confirms that bortezomib overcomes the adverse prognostic features of the 4;14 translocation. A new observation is that patients with overexpression of the 1q21 gene have a poor prognosis.

Bortezomib with Thalidomide plus Dexamethasone Compared with Thalidomide plus Dexamethasone as Induction Therapy Before, and Consolidation Therapy After, Double Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Randomized Phase 3 Study

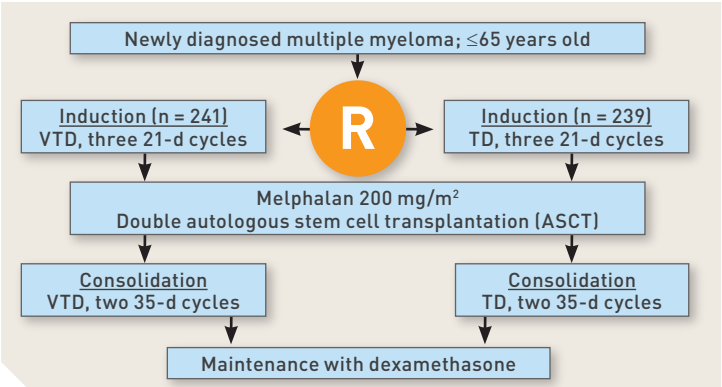
Cavo M et al.
Lancet 2010;376(9758):2075-85.

Response to Induction Therapy Intent-to-Treat Analysis

	VTD (n = 236)	TD (n = 238)	*p*-value
Complete response (CR)	19%	5%	<0.0001
CR + near CR (nCR)	31%	11%	<0.0001
≥Very good partial response	62%	28%	<0.0001
≥Partial response	93%	79%	0.0011
Minimal response or stable disease	7%	16%	0.0011
Progressive disease	0%	5%	0.005

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Trial Schema



Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Response After Second ASCT

	VTD (n = 236)	TD (n = 238)	*p*-value
CR	42%	30%	0.0105
CR + nCR	55%	41%	0.0024
≥Very good partial response	82%	64%	<0.0001
≥Partial response	93%	84%	<0.0011
Minimal response or stable disease	6%	8%	0.38
Progressive disease	1%	8%	0.0001

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Progression-Free Survival (PFS) in Patients with Poor Prognoses

	VTD	TD	*p*-value
Estimated 3-year PFS	68%	56%	0.0057
Events/number of patients			
Presence of del(13q)	29/103	46/103	0.0039
LDH >190 U/L	43/182	72/200	0.0088
Age >60 years	23/92	41/95	0.0150
Presence of t(4;14) ± del(17p)	20/53	32/57	0.0174
Bone marrow plasma cells >50%	30/116	41/111	0.0301
ISS disease Stage II–III	42/129	57/131	0.0482

LDH = lactate dehydrogenase

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Author Conclusions

> In this patient population induction and consolidation therapy with VTD significantly improved clinical outcomes compared to TD therapy in those receiving double ASCT.
> – CR/nCR rate: 31% (VTD) versus 11% (TD); *p*-value < 0.0001
> VTD combined with double ASCT had a positive effect on PFS in patients with poor prognoses, including those with adverse cytogenetic abnormalities who do not benefit from standard ASCT.
> VTD represents a new standard to maximize the degree and speed of tumor reduction in patients with myeloma who are eligible for transplant.

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Select Grade 3 or 4 Adverse Events (AEs) During Induction Therapy

	VTD (n = 236)	TD (n = 238)	*p*-value
Any serious AE	13%	13%	0.86
Any Grade 3 or 4 AE	56%	33%	<0.0001
Any Grade 3 or 4 non-hematologic AE	51%	31%	<0.0001
Peripheral neuropathy (PN)*	10%	2%	0.0004
Skin rash	10%	2%	0.0001
Gastrointestinal events	2%	<1%	0.0982

* Resolution or improvement of severe PN was recorded in 18 of 23 patients receiving VTD and in 3 of 5 patients receiving TD.

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

Faculty Comments

DR ZONDER: This up-front study randomly assigned patients with multiple myeloma eligible for transplant to VTD or TD. The study demonstrated that VTD was superior overall to TD. The percent of patients who had a complete response (CR) or near CR (nCR) after induction was 3 times higher on the VTD arm, and the rate of partial response or better was 93% versus 79%. That benefit seems to carry through transplant. Outside the setting of a study, it appears that VTD is superior to TD, but even with that combination, you can improve responses in patients who aren't in a CR or nCR by sending them for transplant.

Stem Cell Mobilization in Patients with Newly Diagnosed Multiple Myeloma After Lenalidomide Induction Therapy

Cavallo F et al.
Leukemia 2011;25(10):1627-31.

Methods and Objective

> Rd induction therapy was administered in a multicenter, prospective study (RV-MM-PI209) for patients with newly diagnosed MM.

> Patients were then mobilized and randomly assigned to receive oral MPR (melphalan/prednisone/lenalidomide) or high-dose melphalan and tandem autologous stem cell transplant (ASCT).

> The objective of this study was to investigate the influence of 4 cycles of Rd induction therapy on stem cell collection.

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Background

> The mobilization of stem cells may be adversely affected by cytopenias associated with the use of lenalidomide in patients with multiple myeloma (MM).

> Median yield of stem cells collected after lenalidomide/dexamethasone (Rd) induction is lower in patients mobilized with granulocyte-colony stimulating factor (G-CSF) alone compared to patients mobilized with cyclophosphamide and G-CSF (*Leukemia* 2007;21:2035).

> The hematologic toxicity observed during treatment with lenalidomide has raised concern that its use may negatively affect the ability to mobilize stem cells (*Leukemia* 2007;21:2035).

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Stem Cell Harvest — All Evaluable Patients

	n = 331
Median duration of leukapheresis	3 days
Median cells collected after 1 mobilization cycle (x 10^6 $CD34^+$/kg)	7.8
Median cells collected after 2 mobilization cycles (x 10^6 $CD34^+$/kg)	8.7
Patients with yields <2 x 10^6 $CD34^+$/kg at 1st mobilization*	15%
Patients with yields <4 x 10^6 $CD34^+$/kg at 1st mobilization	21%
Patients with yields <2 x 10^6 $CD34^+$/kg at 2nd mobilization	8%
Patients with yields <4 x 10^6 $CD34^+$/kg at 2nd mobilization	9%

* Inadequate yield defined as <4x10^6 $CD34^+$/kg

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Engraftment at First ASCT

	n = 143*
Median x 10^6 $CD34^+$/kg cells infused	4.30
Days until absolute neutrophil count >500 x 10^9/L Median	8
Days until platelet count >25 x 10^9/L Median	7.5
Red blood cell transfusion	36%
Platelet transfusion	59%

* Patients in the evaluable population who received Rd induction therapy

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Author Conclusions

> Lenalidomide as part of an induction regimen did not adversely affect stem cell mobilization.

> The quantity of stem cells collected was adequate to perform tandem ASCT in 91% of patients with rapid and successful engraftment in all patients.

> This is the largest prospective study reporting on stem cell collection after Rd induction before ASCT in patients with newly diagnosed MM.

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Stem Cell Mobilization Summary

Inadequate yield after first mobilization	21%
Inadequate yield after second mobilization	9%
Patients able to obtain sufficient stem cell harvests (at the end of the mobilization phase)	**91%**

Cavallo F et al. *Leukemia* 2011;25(10):1627-31.

Faculty Comments

DR ZONDER: Concerns have arisen in the literature about the impact of lenalidomide on stem cell collection. This study evaluated 346 patients with newly diagnosed multiple myeloma who received 4 cycles of lenalidomide/dexamethasone (Rd) followed by stem cell collection with cyclophosphamide and G-CSF.

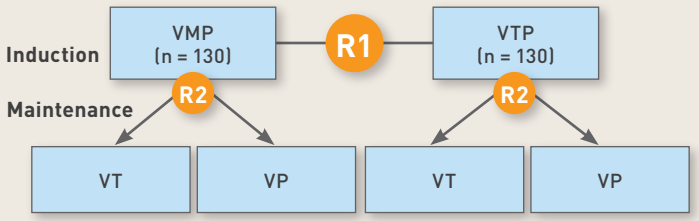
The authors reported that 79% of patients achieved sufficient yield with first mobilization. Upon second mobilization, 91% of patients achieved adequate yield.

The bottom line is we now have data that indicate that lenalidomide exposure does not have an effect on ability to mobilize stem cells and that the majority of patients are able to be adequately mobilized with 1 or 2 collection attempts.

Bortezomib, Melphalan, and Prednisone versus Bortezomib, Thalidomide, and Prednisone as Induction Therapy Followed by Maintenance Treatment with Bortezomib and Thalidomide versus Bortezomib and Prednisone in Elderly Patients with Untreated Multiple Myeloma: A Randomized Trial

Mateos MV et al.
Lancet Oncol 2010;11(10):934-41.

VMP vs VTP Followed by VT vs VP for Untreated MM in Patients >65 Years



Bortezomib (V): Induction phase, 1.3 mg/m^2 twice weekly during a 6-week first cycle, then weekly during subsequent cycles; maintenance phase, 1.3 mg/m^2 twice weekly days 1, 4, 8 and 11 every 3 months

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Introduction

> Bortezomib, melphalan and prednisone (VMP) is tolerable and effective in elderly patients with multiple myeloma (MM).
- 89% ≥overall response rate (ORR); 32% complete response (CR) (*Blood* 2006;108:2165)
- Median progression-free survival = 27.2 months (*Haematologica* 2008;93:560)
- 17% Grade 3 or 4 peripheral neuropathy

> Current study objectives
- Induction: To achieve a CR rate of ≥20% and to determine whether melphalan or thalidomide was better in combination with bortezomib
- Maintenance: To increase CR rate by ≥15% (from 20% after induction to 35%) with a favorable toxicity profile

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Response Rate During Induction and Maintenance Therapy

Induction therapy	VMP (n = 130)	VTP (n = 130)	*p*-value
ORR (≥PR)	80%	81%	0.9
CR	20%	28%	0.2
Near CR	12%	8%	0.2
PR	48%	45%	0.7
Maintenance therapy	**VP (n = 87)**	**VT (n = 91)**	***p*-value**
CR	39%	44%	NS

NS = not significant

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Response in Hyperdiploid (HD) versus Nonhyperdiploid (NHD) Patients

Response	NHD (n = 92)	HD* (n = 132)	*p*-value
ORR	77%	83%	0.4
VMP group	82%	81%	0.7
VTP group	73%	86%	0.4
3-year overall survival (95% CI)	63%	77%	0.04
VMP group	72%	76%	0.5
VTP group	53%	77%	0.02

* HD patient group: DNA index >1.0 with assessments performed by flow cytometry

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Author Conclusions

> Reduced-intensity induction with a bortezomib-based regimen, followed by maintenance, is a safe and effective treatment for elderly patients with MM.
> – ORR, 80% (VMP) versus 81% (VTP); *p*-value = 0.9

> The rates of Grade 3 or worse peripheral neuropathy and gastrointestinal symptoms were similar compared to a conventional schedule of VMP.

> Maintenance therapy increased CR rates (VP: 39% versus VT: 44%).

> In contrast to VMP, VTP induction was associated with a higher occurrence of serious AEs.

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Select Adverse Events (AEs) (Grade 3 or Worse)

Induction therapy	VMP (n = 130)	VTP (n = 130)	*p*-value
Thrombocytopenia	27%	12%	0.0001
Neutropenia	39%	22%	0.008
Peripheral neuropathy	7%	9%	0.6
Related serious AEs	15%	31%	0.01
Maintenance therapy	**VP (n = 87)**	**VT (n = 91)**	***p*-value**
Thrombocytopenia (Grade 1 or 2)	1%	1%	0.8
Gastrointestinal toxicity	1%	4%	0.6
Peripheral neuropathy	2%	7%	0.6
Discontinuation due to AEs	5%	8%	0.6

Mateos MV et al. *Lancet Oncol* 2010;11(10):934-41.

Faculty Comments

DR ZONDER: This study investigated the benefits and importance of: (1) sequenced drugs such as melphalan, (2) simultaneous treatment with bortezomib and thalidomide and (3) the inclusion of maintenance therapy in the treatment regimen. The study demonstrated that the 2 induction treatment regimens induced a higher response rate than that previously observed with TD in the same patient population. Therefore, either VMP or VTP would be considered as reasonable alternatives to TD therapy. However, VTP produced more toxic effects than VMP.

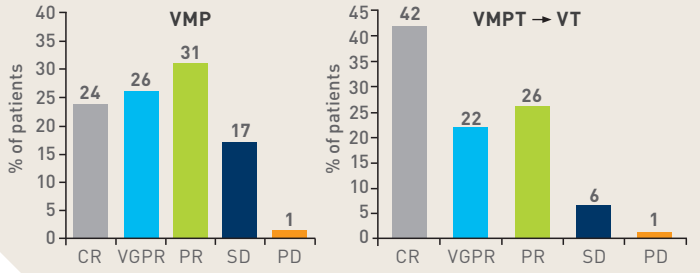
DR WOLF: This is an important study because of the elderly population evaluated. My take-home message from this study is that continued therapy with bortezomib is effective and a reasonable consideration.

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

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

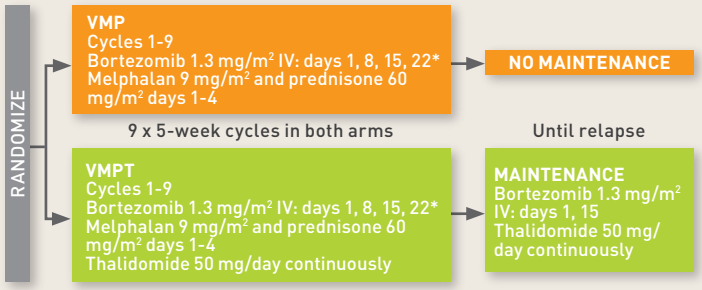
Best Response Rates

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



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

Study Schema



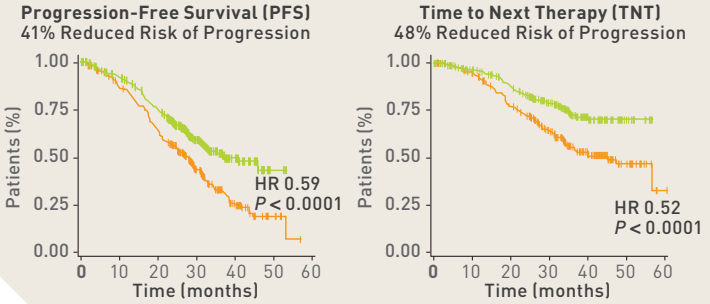
* 66 VMP patients and 73 VMPT patients received twice-weekly infusions of bortezomib

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

Results: Progression-Free Survival and Time to Next Therapy

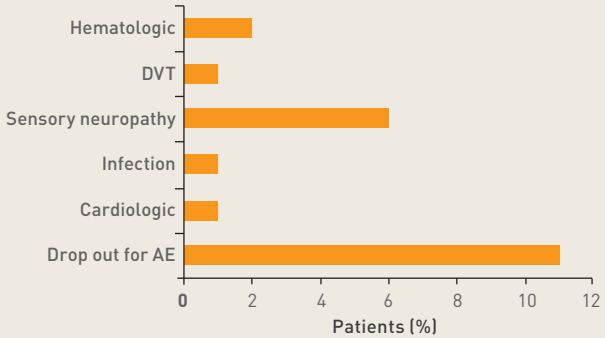
	3-years PFS	Median PFS
VMPT	51%	37.2 months
VMP	32%	27.4 months

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



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

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



Newly occurring or worsening Grade 3 or 4 adverse events

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

Author Conclusions

> Statistically significant improvements reported with VMPT → VT versus VMP for the treatment of newly diagnosed multiple myeloma.
  – CR rate: 42% versus 24% ($p < 0.0001$)
  – Median PFS: 37 months versus 27 months ($p < 0.0001$)
> VMPT → VT prolonged PFS with an unprecedented 3-year PFS of 51% in elderly patients.
> Higher dose-intensity regimens seemed to be less effective in frail patients (≥75 years) (data not shown).
> Maintenance therapy with VT further improved PFS with a good safety profile.

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

Efficacy and Toxicity by Bortezomib Schedule

	VMP twice weekly* (in VISTA)	VMP twice weekly	VMP once weekly
Complete response (CR)	30%	27%	23%
3-year progression-free survival (PFS)	NA	32%	35%
Sensory peripheral neuropathy (PN)			
Any grade	44%	43%	21%
Grade 3 or 4	13%	14%	2%
PN discontinuation	NA	16%	4%

* Mateos MV et al. *J Clin Oncol* 2010;28(13):2259-66.
NA = not applicable

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

Faculty Comments

DR ZONDER: The take-home messages in this study are (1) VMPT had a statistically significant and clinically somewhat significant increase in the overall response rate and (2) I believe the most impressive difference between these arms was the percent of deep responses and the PFS. The PFS benefit has everything to do with maintenance therapy.

DR WOLF: Probably the most important aspect of this study wasn't planned initially. Some patients on this trial were switched from twice-weekly to once-weekly bortezomib. The important observation here is that in both groups, the once-weekly infusion reduced the incidence of severe peripheral neuropathy from 4% to 2%, which is huge.

Phase 3b UPFRONT Study: Safety and Efficacy of Weekly Bortezomib Maintenance Therapy After Bortezomib-Based Induction Regimens in Elderly, Newly Diagnosed Multiple Myeloma Patients

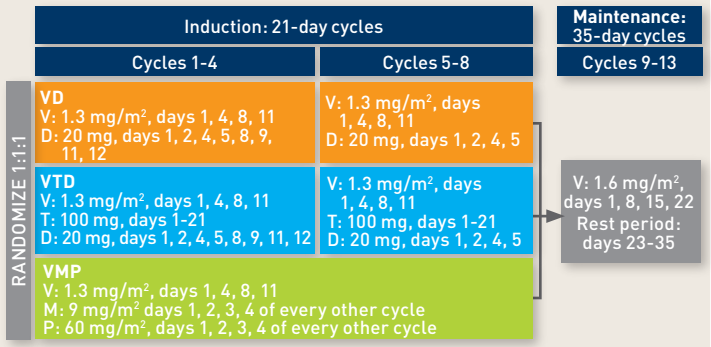
Niesvizky R et al.
Proc ASH 2010;Abstract 619.

Study Design

> Key inclusion criteria:
> Patients ≥18 years with previously untreated symptomatic multiple myeloma
> Karnofsky performance status score ≥50%
> Measurable disease requiring systemic therapy
> Key exclusion criterion:
> Grade ≥2 peripheral neuropathy (PN) within 21 days prior to enrollment
> Concomitant prophylaxis:
> VTD arm: Aspirin, full-dose warfarin or low molecular weight heparin unless medically contraindicated
> All groups: Prophylaxis for herpes zoster recommended

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

UPFRONT Study Schema



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

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

Efficacy: Survival and Response Rates

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

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

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

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

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

Treatment Emergent Grade ≥3 Adverse Events (AEs)

	VD		VTD		VMP	
	I (n = 99)	M (n = 55)	I (n = 93)	M (n = 31)	I (n = 99)	M (n = 43)
At least 1 Grade ≥3 AE	70%	7%	84%	6%	79%	2%
PN	15%	5%	26%	6%	20%	2%
Fatigue	8%	4%	15%	0%	8%	0%
Neutropenia	1%	0%	3%	0%	21%	0%
Diarrhea	8%	5%	4%	3%	7%	7%
Pneumonia	11%	0%	6%	0%	4%	5%

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

Author Conclusions

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

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

Peripheral Neuropathy

	VD (n = 99)		VTD (n = 93)		VMP (n = 99)	
	I (n = 99)	M (n = 55)	I (n = 93)	M (n = 31)	I (n = 99)	M (n = 43)
Any grade PN resulting in discontinuation of all study drugs	7%	4%	18%	0%	18%	0%
Grade ≥3 PN resulting in discontinuation of all study drugs	4%	4%	13%	0%	14%	0%
Median time to PN	77 days		41 days		63 days	

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

Faculty Comments

DR ZONDER: This study evaluated VD versus VTP versus VMP followed by 25 weeks of weekly maintenance bortezomib in all arms. All 3 bortezomib-based regimens resulted in substantial efficacy after 8 cycles. Overall response rates were 68% (VD), 78% (VTP) and 71% (VMP). Response rates were comparable (increased 1% to 3%) after bortezomib maintenance, but I don't believe that's all that surprising.

DR WOLF: The take-home message in this study is that 3-drug regimens are marginally better than 2-drug regimens, and you can continue bortezomib weekly. Response rates improved after bortezomib maintenance, with no increase in the incidence of peripheral neuropathy.

The Efficacy and Safety of Lenalidomide and Dexamethasone in Relapsed and/or Refractory Multiple Myeloma Patients with Impaired Renal Function

Dimopoulos M et al.
Cancer 2010;116(16):3807-14.

Introduction

> 20% of patients with multiple myeloma (MM) present with renal failure[1], which is the second most common cause of death in patients with MM[2] ([1] *Leukemia* 2008;22:1485, [2] *Arch Pathol Lab Med* 2004;128:875).
> Recovery of renal function can occur through therapeutic control of MM and is associated with an improvement in outcome (*Arch Intern Med* 1998;158:1889).
> Lenalidomide (LEN) with dexamethasone (DEX) is an effective therapy for MM associated with an overall response rate of 60% (*N Engl J Med* 2007;357:2133).
> Current study objective:
– Assess the effect of renal dysfunction on safety and efficacy outcomes of patients treated with lenalidomide

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Study Methods

> Retrospective analysis of 350 patients randomly assigned to receive LEN with DEX in MM-009 and MM-010 Phase III trials

> Renal function was assessed throughout the study by measurement of serum creatinine levels and calculation of creatinine clearance (CL_{cr}).

> CL_{cr} values were used to subdivide patients into renal impairment (RI) subgroups
– Mild or no RI = CL_{cr} ≥60 mL/minute
– Moderate RI = CL_{cr} ≥30 mL/minute and <60 mL/minute
– Severe RI = CL_{cr} <30 mL/minute

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Efficacy Outcomes According to Renal Function

Clinical parameter	Mild or no RI (n = 243)	Moderate RI (n = 82)	Severe RI (n = 16)
Overall response Complete response Very good partial response Partial response	64% 16% 19% 30%	56% 16% 11% 29%	50% 6% 31% 13%
Median time to progression	12.0 mo	11.1 mo	7.8 mo
Median progression-free survival	11.1 mo	9.5 mo	7.8 mo
Median overall survival	38.9 mo	29.0 mo*	18.4 mo*

* Includes "response was not evaluable" patients and those without response assessment; $p = 0.006$ versus mild or no RI

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Dosage Information According to Renal Function

Variable	Mild or no RI (n = 243)	Moderate RI (n = 82)	Severe RI (n = 16)
Median LEN dose	25 mg/d	25 mg/d	15 mg/d*
Dose reduction/interruption due to adverse event	22%	40%*	38%*
Median time to LEN dose reduction	99 days	85 days	78 days
Discontinuation due to adverse event	12%	18%	38%*

* $p < 0.05$ versus patients with mild or no RI

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Author Conclusions

> With careful monitoring of the CL_{cr} level and adverse events and undertaking the appropriate dose adjustments, LEN with DEX is an effective and well-tolerated treatment option for patients with MM and RI.

> Patients with moderate to severe RI:
- Had increased incidence of thrombocytopenia (data not shown)
- Required more frequent LEN dose reduction/interruption
- Had shorter overall survival

> Formal studies confirming the efficacy of LEN in patients with renal failure are warranted and ongoing.

> For future studies of LEN, it is important to convert serum creatinine to CL_{cr} and to use CL_{cr} for recommended LEN dosage adjustments for patients with RI.

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Recommendations for LEN Dosing in Patients with MM and Renal Impairment*

Category	Renal function†	LEN dosing in MM
Moderate RI	CL_{cr} ≥30 mL/min to <60 mL/min	10 mg every 24 h
Severe RI	CL_{cr} <30 mL/min (not requiring dialysis)	15 mg every 48 h
End-stage renal disease	CL_{cr} <30 mL/min (requiring dialysis)	5 mg once daily; on dialysis days, dose administered after dialysis

* Based on LEN prescribing information
† Cockcroft-Gault CL_{cr}

Dimopoulos M et al. *Cancer* 2010;116(16):3807-14.

Faculty Comments

DR BENSINGER: Compared to patients with mild or no renal dysfunction, patients with moderate to severe renal dysfunction did not live as long and their disease progressed faster. With the proper dose adjustments, this study demonstrated that lenalidomide was safe and effective for patients with renal impairment. I had a patient with multiple myeloma who developed rapidly progressive renal failure. We were able to improve his renal function and bring him back into remission using low-dose lenalidomide at 5 mg, followed by 10 mg.

DR WOLF: The message here is that you can use lenalidomide in this setting. If I opt to do so, I start at a low dose. If the patient's counts are fine, I'll raise the dose. You have to be careful and you have to adjust your dose.

Guidelines for Standard Investigative Workup: Report of the International Myeloma Workshop Consensus Panel 3

Dimopoulos M et al.
Blood 2011;117(18):4701-5.

Diagnostic Criteria for Plasma Cell Disorders

> **Monoclonal gammopathy of undetermined significance***:
  – Serum monoclonal protein <3 g/dL
  – Clonal bone marrow plasma cells <10%
  – Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder
> **Smoldering MM (asymptomatic MM)***:
  – Serum monoclonal protein (IgG or IgA) ≥3 g/dL and/or clonal bone marrow plasma cells ≥10%
  – Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia or renal failure that can be attributed to a plasma cell proliferative disorder

*** All/both criteria must be met**

Dimopoulos M et al. *Blood* 2011;117(18):4701-5.

Introduction

> In everyday practice, confusion remains regarding the use of standard laboratory tests that evaluate serum and urine monoclonal proteins.
> During the past decade, newer imaging techniques, such as MRI and PET/CT, have been increasingly used in the assessment of patients with multiple myeloma (MM).
> This report from the International Myeloma Working Group Consensus Panel contains recommendations for the minimum diagnostic and prognostic tests, the follow-up investigation after therapy and the tests to be performed at relapse for patients with MM.

Dimopoulos M et al. *Blood* 2011;117(18):4701-5.

Diagnostic Criteria for Plasma Cell Disorders (continued)

> **Symptomatic MM***:
  – Clonal bone marrow plasma cells ≥10%
  – Presence of serum and/or urinary monoclonal protein (except in patients with nonsecretory MM†)
  – Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    • Hypercalcemia
    • Renal insufficiency
    • Anemia
    • Bone lesions

*** All 3 criteria must be met except as noted above**

† ≥10% clonal plasma cells are required for the diagnosis of nonsecretory myeloma

Dimopoulos M et al. *Blood* 2011;117(18):4701-5.

Laboratory Tests for Initial Investigation of Suspected MM

> History and physical examination
> Complete blood count and differential; peripheral blood smear
> Chemistry screen including calcium and creatinine
> Serum protein electrophoresis, immunofixation
> Nephelometric quantification of serum immunoglobulins
> 24-hour urine collection for electrophoresis and immunofixation
> Bone marrow aspirate and/or biopsy
> Cytogenetics (metaphase karyotype and FISH)
> Radiological skeletal bone survey including spine, pelvis, skull, humeri and femurs; MRI in certain circumstances
> Serum β2 microglobulin and LDH
> Measurement of serum free light chains

Dimopoulos M et al. *Blood* 2011;117(18):4701-5.

Tests to Be Performed at Relapse

> The majority of the workup recommended at diagnosis is also pertinent at relapse.
> A bone marrow aspirate and/or biopsy should be performed if clinically indicated (ie, suspicion of hyposecretory MM progression or when MDS is considered [presence of cytopenias]).
> For patients with normal or no cytogenetic or FISH analyses at baseline, these tests should be performed at relapse.
> A skeletal survey may be indicated to detect possible lesions at risk for fracture.
> Other imaging studies (CT, MRI, PET/CT) to detect soft tissue masses arising from bone lesions or extramedullary disease may be indicated according to clinical circumstances.

Dimopoulos M et al. *Blood* 2011;117(18):4701-5.

Follow-Up Treatment

The majority of the laboratory tests indicated for initial assessment are to be repeated during follow-up.

Exceptions as follows:

> For most patients: No necessity for bone marrow examination to assess response provided that the disease can be monitored with serum and urine studies and no indication is present to change the patient's treatment
> No indication to repeat the metaphase karyotype, FISH studies or flow cytometric studies as a routine follow-up
> No need to repeat skeletal survey in a patient who is responding to treatment unless he/she develops bone symptoms

Dimopoulos M et al. *Blood* 2011;117(18):4701-5.

Faculty Comments

DR WOLF: One of the most important aspects of this 2009 International Myeloma Workshop Consensus Panel was the recommendation for more liberal use of the free light chain assay. Another recommendation was for use of FISH analysis for all patients.

Although I tend to disagree, the panel's last statement indicates that skeletal survey remains the standard method for imaging, but MRI provides valuable diagnostic information. When the proceedings from the 2011 workshop in Paris are published, I believe we'll see a stronger statement on the recommended use of MRI and PET.

Guidelines for Risk Stratification in Multiple Myeloma: Report of the International Myeloma Workshop Consensus Panel 2

Munshi NC et al.
Blood 2011;117(18):4696-700.

Risk Stratification: Purpose

> Risk stratification:
  – Should only be used to determine prognosis and treatment stratification
  – Does not indicate therapy initiation
  – Does not indicate therapy selection

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Introduction

> Multiple myeloma is a heterogeneous disease with a variable disease course and survival ranging from <1 year with aggressive disease to >10 years with disease that is indolent at presentation.
> Evaluation of prognostic factors and risk stratification is important in defining treatment strategies, in the comparison of outcomes of therapeutic trials and in predicting survival.
> Risk stratification aspects evaluated by the consensus panel:
  – Purpose and timing, especially at diagnosis and relapse
  – Relationship to therapy and clinical and laboratory features, including genomic changes used to stratify patients and predict outcome

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Risk Stratification: Timing

> Timing
  – Diagnosis:
    • All current risk stratification is applicable to patients with newly diagnosed disease.
  – Relapse:
    • Change in risk factors at relapse has been documented, and the same genetic abnormalities characteristic of poor outcome at diagnosis may suggest poor outcome if detected at relapse.
    • Patients with good risk at diagnosis should be evaluated for high-risk features at relapse.

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Risk Stratification Factors

> Detection of any cytogenetic abnormality is considered to suggest higher-risk disease.
> Cytogenetics with specific abnormalities and FISH with specific markers need to be performed on bone marrow samples.
> Poor risk, cytogenetically detected:
  – Chromosomal 13 or 13q deletion
  – t(4;14)
  – del(17p)
> Poor risk, FISH detected:
  – t(4;14)
  – t(14;16)
  – del(17p)

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Investigation for Risk Stratification

> Recommended investigation:
  – Serum albumin and β2M to determine ISS stage
  – Bone marrow examination for t(4;14), t(14;16) and del(17p) on identified plasma cells by FISH
  – LDH
  – Immunoglobulin type — IgA
  – Histology — plasmablastic disease
> Additional investigation:
  – Cytogenetics
  – Gene expression profiling
  – Labeling index
  – MRI/PET scan
  – DNA copy number alteration by CGH/SNP array

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Risk Stratification Factors (continued)

> Predictors of high-risk disease:
  – High serum β2M level
  – ISS Stage II and III incorporating high β2M
  – Low albumin
> Additional individual risk factors (unknown applicability, with no indication for change in treatment approach):

LDH	IgA
Extramedullary disease	Renal failure
High serum free light chain	Plasmablastic disease
Plasma cell leukemia	Serum free κ/λ ratio

Munshi NC et al. *Blood* 2011;117(18):4696-700.

Faculty Comments

DR BENSINGER: The panel confirmed what is known in the myeloma community — that certain features, such as serum albumin and the ISS staging that includes β2M, have been shown to be important for stratifying high versus low risk. Also, the cytogenetic abnormalities we have been aware of for several years have important prognostic value and convey high-risk features. It was also agreed that although certain features have been shown in some studies to be important for prognosis, the data were not enough to include in risk stratification at present. These include chromosome 1q abnormalities, gene expression and SNP arrays. The need is recognized for global standardization of gene expression and SNP arrays. These assays are not yet ready for widespread use for all patients with myeloma.

Phase 2 Randomized Open Label Study of 2 Modalities of Pomalidomide plus Low-Dose Dexamethasone in Patients with Multiple Myeloma, Refractory to Both Lenalidomide and Bortezomib. IFM 2009-02

Leleu X et al.
Proc ASH 2010;Abstract 859.

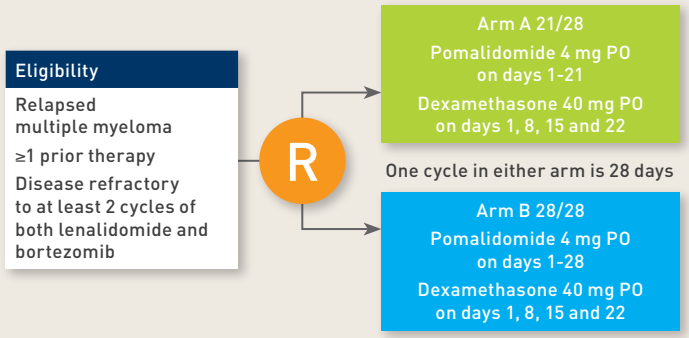
Study Objectives

Primary objective:
- Response rate (partial response and better) according to International Myeloma Working Group in either arm

Secondary objectives (in either arm):
- Safety
- Time to response and duration of response
- Time to disease progression and event-free survival
- Overall survival
- Cytogenetic response in bone marrow plasma cells

Leleu X et al. *Proc ASH* 2010;Abstract 859.

IFM 2009-02 Phase II Study Schema



Leleu X et al. *Proc ASH* 2010;Abstract 859.

Efficacy Assessment (Intent to Treat)

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
Overall response rate (≥partial response)	42%	39%
Stable disease	46.5%	51%
Time to best response	2.0 months	1.7 months
Time to progression, median*	7.0 months	9.7 months

* Median follow-up was 6.5 months for Arm A and 7 months for Arm B.

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Hematologic Adverse Events (AEs)

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
≥Grade 3 events	23.5%	26.5%
Hematologic events	66.0%	76.0%
Hemoglobin ≤8 g/dL	11.0%	14.0%
Neutrophils ≤1 x 10^9/L	34.0%	33.5%
Platelets ≤50 x 10^9/L	18.0%	21.0%

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Author Conclusions

> Pomalidomide and dexamethasone combination provides responses in patients with advanced myeloma refractory to bortezomib and lenalidomide.

> Pomalidomide 4 mg once daily is well tolerated.

> Pomalidomide 4 mg once daily x 21 q4wk does not appear inferior to pomalidomide 4 mg once daily x 28 q4wk.

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Select Nonhematologic AEs

	Arm A (21/28) (n = 43)	Arm B (28/28) (n = 41)
Percentage nonhematologic AEs out of all AEs	12.0%	9.0%
Neuropathy	0%	0%
Deep vein thrombosis (with prophylactic treatment)	0%	0%
Asthenia	9.3%	4.9%
Cramps	0%	4.9%
Diarrhea	0%	4.9%

Leleu X et al. *Proc ASH* 2010;Abstract 859.

Faculty Comments

DR BENSINGER: The third-generation IMiD pomalidomide is a promising new agent and is much more potent than prior generations of immunomodulating drugs. The effective doses of pomalidomide (2 to 4 mg daily) are much lower than the typical doses of thalidomide and lenalidomide. Studies have shown that pomalidomide in combination with dexamethasone or alone is effective at controlling disease in patients for whom a proteasome inhibitor or, in many cases, lenalidomide has failed. So pomalidomide can be effective even when a similar immunomodulatory agent has failed. Toxicity profiles appear similar to other IMiDs in that cytopenias seem to be the major toxicities associated with this agent. So reductions in hemoglobin or reductions in platelet levels or neutrophils are common toxicities.

Pomalidomide plus Low-Dose Dexamethasone in Myeloma Refractory to Both Bortezomib and Lenalidomide: Comparison of Two Dosing Strategies in Dual-Refractory Disease

Lacy MQ et al.
Blood 2011;118(11):2970-5.

Introduction

> Pomalidomide/dexamethasone (pom/dex) regimen using a pom dose of 2 mg/day has demonstrated response rates of:
  – 63% in relapsed multiple myeloma (*JCO* 2009;27:5008)
  – 47% in lenalidomide-refractory cohort (*Leukemia* 2010;24:1934)
> Pom has been evaluated at doses of 4 mg, either continuously or for 21 of 28 days as salvage therapy for patients with relapsed myeloma (*Proc ASH* 2010;Abstract 864; *Proc ASH* 2010;Abstract 859).
> Two sequential Phase II trials were opened to evaluate the efficacy of a pom/dex regimen using 2 different doses of pom in patients with multiple myeloma refractory to both lenalidomide and bortezomib.

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

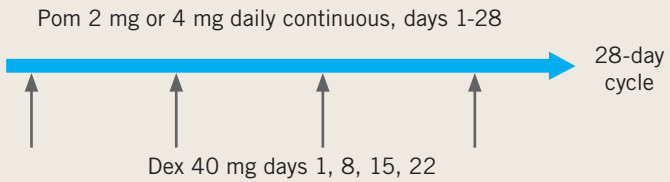
Study Methods

> Two sequential Phase II trials opened with 35 patients each:
  – May 2009-Nov 2009: 2 mg/day pom cohort
  – Nov 2009-Apr 2010: 4 mg/day pom cohort
> Efficacy rule for 2 mg pom cohort:
  – Cohort considered ineffective if a maximum 18 confirmed responders observed in the first 33 evaluable patients
> Efficacy rule for 4 mg pom cohort:
  – Cohort considered ineffective if a maximum 11 confirmed responders observed in the first 33 evaluable patients
> Responses were assessed according to IMWG criteria.

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Treatment Schema

Eligibility
> Previously treated multiple myeloma refractory to lenalidomide and bortezomib



Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Efficacy Assessment

Clinical variable	Pom 2 mg (n = 35)	Pom 4 mg (n = 35)
Confirmed response (≥PR)	26% (9)	28% (10)
≥MR	49%	43%
Median time to response	1 mo	2 mo
Median duration of response	Not reached	3.9 mo
Survival rate at 6 months	78%	67%

PR = partial response; MR = minimal response
- Prespecified efficacy rule for study design was not met by either cohort.
- Of 62 patients with cytogenetics/FISH data available, responses were seen in 13 patients considered to be at high risk (21%).

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Author Conclusions

> Although the study design goals were not met for either cohort, pom/dex was significantly active in dual-refractory myeloma at both dosing levels, and responses were durable.

> Pom/dex demonstrated activity in patients with dual-refractory multiple myeloma who were considered to be at high risk.

> Myelosuppression was the most common toxicity.

> It is not clear whether an advantage exists with the higher 4-mg dose of pom versus the 2-mg dose using the day 1-28 schedule.

> Additional studies are ongoing exploring whether a regimen of 4 mg of pom for 21 of 28 days is superior to 2 mg continuously.

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Select Grade 3/4 Adverse Events

Clinical variable	Pom 2 mg (n = 35)	Pom 4 mg (n = 35)
Anemia	26%	26%
Neutropenia	51%	65%
Peripheral sensory neuropathy	0%	3%
Thrombosis	3%	3%
Fatigue	9%	9%

Lacy MQ et al. *Blood* 2011;118(11):2970-5.

Faculty Comments

DR WOLF: I believe that pomalidomide will be another important drug for the treatment of multiple myeloma. It is a tolerable drug that shows responses in patients with disease that is refractory to lenalidomide. It may be slightly better than lenalidomide in the sense that little neuropathy was observed with pomalidomide.

I don't believe, however, that this study established the correct dose of the drug as being 4 or 2 mg. In the future, it would be interesting to address whether pomalidomide has activity if used before or instead of lenalidomide for patients with multiple myeloma.

Carfilzomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Multiple Myeloma: Initial Results of Phase I/II MMRC Trial

Jakubowiak AJ et al.
Proc ASH 2010;Abstract 862.

Introduction

> Carfilzomib is a novel, irreversible proteasome inhibitor with promising single-agent activity and a favorable toxicity profile in relapsed/refractory multiple myeloma (MM) (*Proc ASCO* 2009;Abstract 8504).
> Additive anti-MM effects have been reported with carfilzomib in combination with lenalidomide and dexamethasone (CRd) in preclinical studies (*Proc ASH* 2009;Abstract 304).
> Lack of overlapping toxicity allows for the use of these agents at full doses and for extended durations in relapsed/refractory MM (*Proc ASH* 2009;Abstract 304).
> Current study goals: To determine the maximum tolerated dose (MTD) and to assess safety and efficacy of CRd in newly diagnosed MM.

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Methods

> Phase I carfilzomib dose-escalation trial
> Carfilzomib as only dose-escalating agent (IV on days 1, 2, 8, 9, 15, 16 in 28-day cycles)
  – Level 1: 20 mg/m^2
  – Level 2: 27 mg/m^2 (initial maximal planned dose)
  – Level -1: 15 mg/m^2 (if needed)
  – Level 3: 36 mg/m^2 (study amendment inclusion after toxicity assessment)
> Lenalidomide 25 mg PO (days 1-21) for all dose levels
> Dexamethasone 40/20 mg PO weekly (cycles 1-4/5-8) for all dose levels

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Methods (continued)

> Phase I/II (target accrual = 36)
> After ≥4 cycles, patients achieving ≥partial response (PR) proceed to stem cell collection (SCC) and autologous stem cell transplant (ASCT).
  – ASCT candidates offered continued CRd treatment after SCC
> After completion of 8 cycles, patients receive 28-day maintenance cycles.
  – Carfilzomib (days 1, 2, 15, 16), lenalidomide days 1-21 and dexamethasone weekly at the doses tolerated at the end of 8 cycles

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Best Responses to Date

Clinical response	CRd (n = 27*)
≥PR	96%
≥Very good PR (VGPR)	70%
Complete response (CR)/near CR (nCR)/ stringent CR	55%

* 4 patients not evaluable for response

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Author Conclusions

> The MTD of carfilzomib was not reached (data not shown).

> CRd is well tolerated and highly active in newly diagnosed MM.
- ≥PR = 96%
- ≥VGPR = 70%
- CR/nCR = 33%

> These data represent the first report to date on treatment of front-line myeloma with carfilzomib and add support to the Phase III trial of CRd versus Rd in relapsed MM (NCT01080391).

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Select Adverse Events (Abstract)

Hematologic	CRd (n = 21)
Neutropenia (Grade 3 or 4)	14%
Thrombocytopenia (Grade 3 or 4)	14%
Anemia (Grade 3)	10%
Nonhematologic (Grade 3)	
Peripheral neuropathy (Grade 3 or 4)	0%
Fatigue	5%
Mood alteration	5%
Glucose elevations	24%
Deep vein thrombosis (while receiving aspirin prophylaxis)	5%

Jakubowiak AJ et al. *Proc ASH* 2010;Abstract 862.

Faculty Comments

DR BENSINGER: Carfilzomib is a promising second-generation proteasome inhibitor. It is more target specific and probably has a lower incidence of off-target side effects, the most notable being peripheral neuropathy. This trial evaluated carfilzomib at the maximum preferred dose of 27 mg/m^2 in combination with lenalidomide and dexamethasone in about 24 patients with newly diagnosed myeloma. Basically, almost 100% of patients responded to treatment. Of the patients enrolled, 23 have remained on the trial. A major degree of peripheral neuropathy has not been reported in this trial. So this regimen yields a high response rate, a high degree of efficacy and a high degree of tolerance. Carfilzomib will be an important agent to add to our armamentarium.

First-Line Treatment with Zoledronic Acid as Compared with Clodronic Acid in Multiple Myeloma (MRC Myeloma IX): A Randomized Controlled Trial

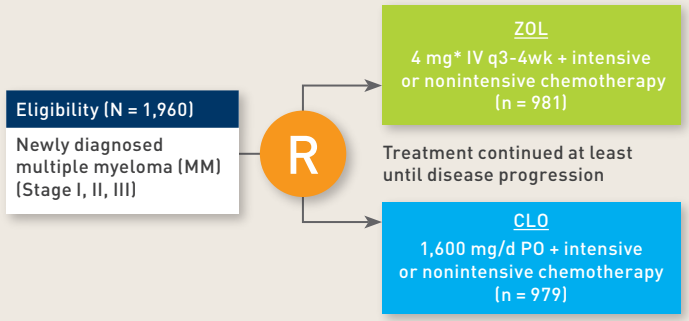
Morgan GJ et al.
Lancet 2010;376(9757):1989-99.

Treatment Status

	ZOL (n = 981)	CLO (n = 979)
Follow-up (median)	3.7 years	3.8 years
Still receiving bisphosphonate (BP)	11%	13%
BP administration not confirmed	6%	4%
Discontinued study before disease progression	24%	19%
Disease progression or death	59%	64%
Time on treatment		
Intensive pathway	396 days	409 days
Nonintensive pathway	320 days	306 days

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

MRC Myeloma IX: A Phase III Trial of Zoledronic Acid (ZOL) versus Clodronic Acid (CLO)



*Dose-adjusted for patients with impaired renal function, per the prescribing information

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Primary Endpoints

Clinical variable	ZOL (n = 981)	CLO (n = 979)	Hazard ratio	*p*-value
Median overall survival	50.0 mo	44.5 mo	0.87	0.04
Median progression-free survival	19.5 mo	17.5 mo	0.91	0.07

Overall response rates did not differ significantly between ZOL and CLO groups

- Patients receiving intensive induction chemotherapy (78% vs 76%; $p = 0.43$)
- Patients receiving nonintensive induction chemotherapy (50% vs 46%; $p = 0.18$)

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Relative Risk Reduction

	Risk reduction	Hazard ratio	*p*-value
Overall survival	16%	0.84	0.0118
Progression-free survival	12%	0.88	0.0179

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Author Conclusions

> ZOL is superior to CLO for the prevention of skeletal-related events (SREs) in patients with newly diagnosed MM.

> Adding ZOL to standard antimyeloma therapy is generally well tolerated and prolongs overall survival vs CLO.
– Survival benefit is independent of SRE reduction.

> These data further support the anticancer activity of ZOL and provide evidence that ZOL should be considered for early integration into treatment regimens for patients with newly diagnosed MM.

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Select Adverse Events (AEs)

AE	Intensive pathway		Nonintensive pathway		Overall *p*-value
	ZOL (n = 555)	CLO (n = 556)	ZOL (n = 428)	CLO (n = 423)	
Osteonecrosis of the jaw (ONJ)	4%	<1%	3%	<1%	<0.0001
Thromboembolic events	19%	15%	12%	8%	0.01
Any serious AE	59%	50%	50%	47%	<0.0001
Infection	9%	11%	4%	7%	0.07
Musculoskeletal, connective tissue, bone disorders	1%	<1%	3%	0%	0.0007

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99.

Faculty Comments

DR BENSINGER: This is a landmark study by the Medical Research Council in the United Kingdom that included all patients with myeloma enrolled in the United Kingdom over a 4-year period between 2003 and 2007. Compared to clodronate (CLO), zoledronic acid (ZOL) extended survival by 5 1/2 months. The absolute time of progression-free interval was about 2 months, but it provided compelling evidence of a direct antimyeloma effect of ZOL. This result underscores that ZOL is one of the most potent of the bisphosphonates. With regard to adverse events, a difference was observed between the 2 groups in the incidence of ONJ — it was 3% to 4% for ZOL versus <1% for CLO. Although ONJ is something you need to be aware of and counsel your patients about, I believe the benefits of using continuous ZOL markedly outweigh the risks.

Does Zoledronic Acid Reduce Skeletal-Related Events and Improve Progression-Free Survival in Patients with Multiple Myeloma with or without Bone Disease? MRC Myeloma IX Study Results[1]

Bisphosphonate Treatment in Multiple Myeloma: Should They Be Used Until Progression?[2]

[1] Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

[2] Davies FE et al. *Proc ASCO* 2011;Abstract 8011.

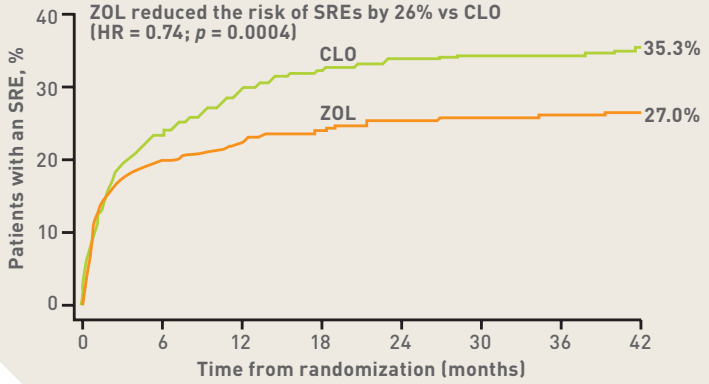
SREs by Baseline Bone Lesion Status

	Patients with an SRE			
Baseline status	**ZOL**	**CLO**	**Hazard ratio**	***p*-value**
Bone lesions at baseline	34%	43%	0.774	0.004
No bone lesions at baseline	9%	17%	0.526	0.007

Highlights the importance of administering treatment to all patients regardless of skeletal morbidity at presentation

Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

Skeletal-Related Events (SREs) — Overall Population



With permission from Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

Author Conclusions — SREs

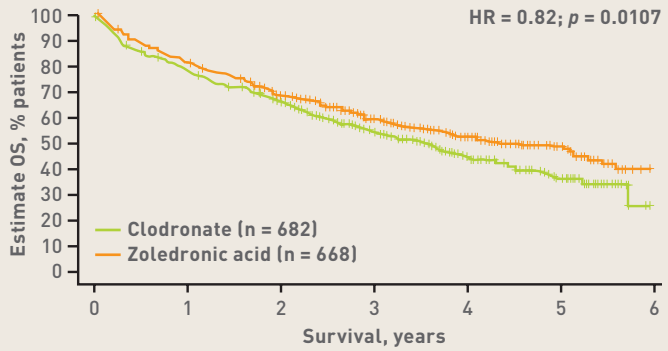
> ZOL significantly reduced the relative risk of SREs vs CLO ($p = 0.0004$).
  – Reductions were documented regardless of bone disease status at presentation.

> SRE rates were higher among patients with preexisting versus no bone disease at presentation.

> SRE reduction with ZOL was apparent within the first year regardless of bone disease status at presentation (data not shown).

Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

Overall Survival (OS)— Patients with Bone Disease at Baseline



With permission from Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

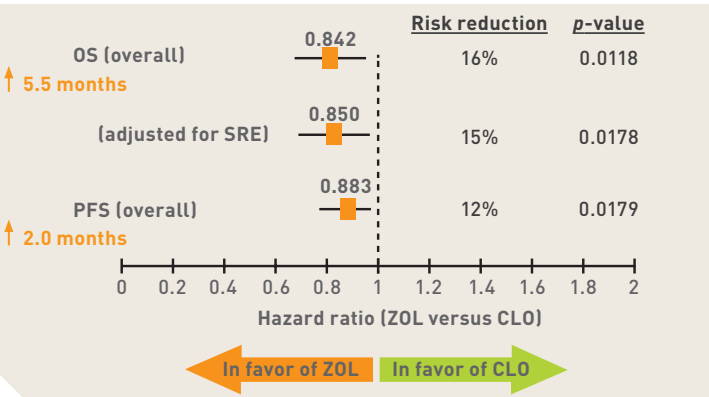
Author Conclusions — Disease Outcomes

> ZOL significantly increased OS and PFS in the overall patient population compared to CLO.
  – OS and PFS benefits appeared limited to the patients with bone disease at presentation (data not shown).
  – The Myeloma IX study was not powered to compare the effects of the treatments on survival in different patient subsets.

> Adverse events were consistent with established safety profiles of the agents (data not shown).

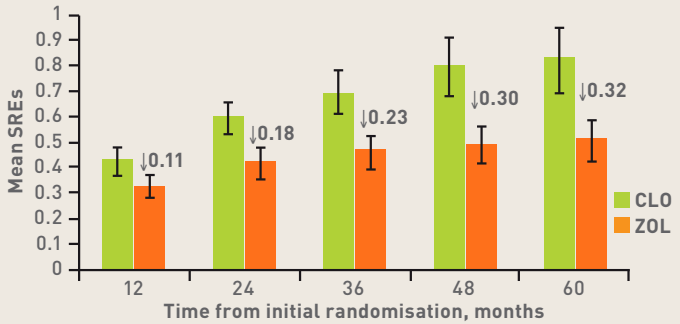
Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

Survival — Overall Population



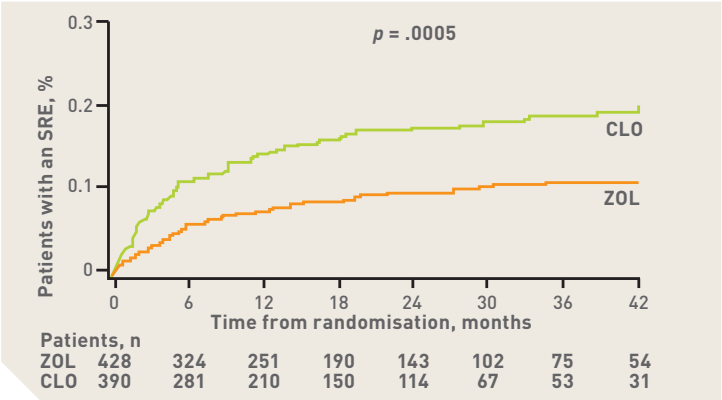
With permission from Boyd K et al. *Proc ASCO* 2011;Abstract 8010.

Multiple Event Analyses — SREs by Year



With permission from Davies FE et al. *Proc ASCO* 2011;Abstract 8011.

ZOL Reduced SREs versus CLO During Maintenance Therapy



With permission from Davies FE et al. *Proc ASCO* 2011;Abstract 8011.

Author Conclusions — Benefit of Bisphosphonates Over Time

> ZOL increases overall survival versus CLO with benefits becoming significant within the first 4 months of treatment.

> ZOL significantly decreased the risk of SREs versus CLO during each of the first 3 years on study, though additional follow-up is needed (data not shown).

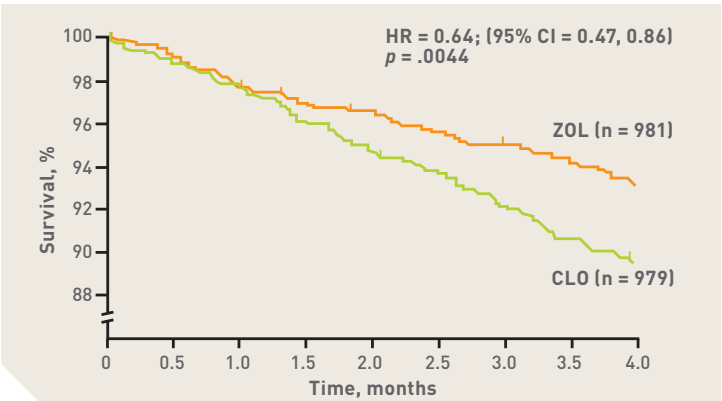
> ZOL significantly decreased the risk of SREs versus CLO during the maintenance portion of the study.

> SRE benefits with ZOL were seen within the first year.

> These analyses support the early initiation of ZOL to prevent SREs and prolong survival, and they support treatment at least until disease progression to provide long-term reduction in SREs.

Davies FE et al. *Proc ASCO* 2011;Abstract 8011.

OS Benefit with ZOL Becomes Significant Early in the Course of Treatment



With permission from Davies FE et al. *Proc ASCO* 2011;Abstract 8011.

Faculty Comments

DR BENSINGER: The use of ZOL resulted in fewer SREs for the entire population. Not only did ZOL reduce bone lesions in patients with preexisting disease, but patients with no bone disease at baseline who received ZOL had fewer SREs. The fact that bisphosphonates can prevent SREs in patients who do not have them at presentation has been reported previously, but the fact that ZOL was superior to CLO is useful to know.

The study by Davies examined the benefit of ZOL over time, focusing on a remarkable aspect of this trial, that patients received bisphosphonates continuously until disease progression. Previously we used a 2-year treatment term based on initial studies. This changed my practice, and I now recommend ZOL throughout the course of the patient's disease.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the Phase III UPFRONT study, which of the following bortezomib-based regimens was shown to be active in the treatment of newly diagnosed MM in elderly patients?**
   a. Bortezomib/melphalan/prednisone
   b. Bortezomib/thalidomide/dexamethasone
   c. Bortezomib/dexamethasone
   d. All of the above
2. **A weekly bortezomib regimen has _____ when compared to a twice-weekly bortezomib regimen in the treatment of MM in elderly patients.**
   a. Similar efficacy and toxicity
   b. Similar efficacy and reduced toxicity
   c. Reduced efficacy and toxicity
3. **In a large, randomized Phase III study for patients with previously untreated myeloma who were eligible for transplant, induction and consolidation therapy with VTD significantly improved clinical outcomes compared to TD therapy in patients receiving double autologous stem cell transplant (ASCT).**
   a. True
   b. False
4. **Data from the CALGB-100104 and IFM 2005-02 trials indicate that lenalidomide maintenance therapy is effective in patients with MM.**
   a. True
   b. False
5. **Updated data presented at the 13th International Myeloma Workshop by the CALGB indicate that patients receiving lenalidomide maintenance therapy experience a(n) _____ risk of developing second cancers compared to patients on the placebo arm.**
   a. Lower
   b. Higher
   c. Equal
6. **Subcutaneous administration of bortezomib for patients with relapsed MM was found to be equivalent to intravenous administration for which of the following efficacy outcomes?**
   a. Overall response rate
   b. Median time to disease progression
   c. One-year overall survival rate
   d. Both a and c
   e. All of the above
7. **The rates of peripheral neuropathy associated with bortezomib were reduced with subcutaneous administration compared to intravenous administration.**
   a. True
   b. False
8. **A retrospective analysis of patients with MM and renal impairment (RI) who received lenalidomide and dexamethasone demonstrated that patients with moderate to severe RI had _____.**
   a. A decreased risk of thrombocytopenia
   b. A shorter overall survival
   c. More frequent lenalidomide dose interruptions/discontinuations
   d. Both a and b
   e. Both b and c
9. **Patients who received zoledronic acid on the MRC Myeloma IX trial experienced a(n) _____ incidence of osteonecrosis of the jaw compared to patients who received clodronate.**
   a. Increased
   b. Decreased
10. **In a Phase I/II MMRC trial evaluating carfilzomib, lenalidomide and dexamethasone for patients with newly diagnosed MM (NDMM), the authors reported a >95% response rate (partial response or better).**
    a. True
    b. False

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
Progression-free survival in response to VTD induction and consolidation with double ASCT in patients with NDMM and poor prognosis	4 3 2 1	4 3 2 1
Efficacy and safety of weekly versus twice-weekly bortezomib in MM	4 3 2 1	4 3 2 1
Clinical benefits and risk of second primary cancers with maintenance lenalidomide in MM	4 3 2 1	4 3 2 1
IFM 2009-02: Response rates of 2 dosing strategies of pomalidomide in combination with low-dose dexamethasone for relapsed/refractory MM	4 3 2 1	4 3 2 1
Efficacy and skeletal-related events with zoledronic acid versus clodronate in NDMM	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: .....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

⬭ This activity validated my current practice; no changes will be made
⬭ Change the management and/or treatment of my patients
⬭ Create/revise protocols, policies and/or procedures
⬭ Other (please explain): .....

If you intend to implement any changes in your practice, please provide 1 or more examples: .....

The content of this activity matched my current (or potential) scope of practice. ⬭ Yes ⬭ No 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:

- Appraise recent data on therapeutic advances and changing practice standards in MM, and integrate this information into the selection of optimal systemic therapy for patients with 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/proteasome inhibitor regimens. ..... 4 3 2 1 N/M N/A
- Utilize biomarkers to risk-stratify patients with MM, and recommend systemic treatment commensurate with prognosis and likelihood of therapeutic response ..... 4 3 2 1 N/M N/A
- Recognize the treatment-associated side effects of bortezomib, and offer patients acceptable alternative dosing/administration and/or supportive management interventions to address them ..... 4 3 2 1 N/M N/A
- Communicate the benefits and risks of postinduction maintenance therapy to appropriately selected patients with MM. ..... 4 3 2 1 N/M N/A
- Consider recent Phase III trial data on the use of bisphosphonates for osteolytic and nonosteolytic MM when selecting frequency of administration and total duration of bisphosphonate therapy. ..... 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

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague? ⬭ Yes ⬭ No If no, please explain: .....

Additional comments about this activity: .....

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YIRMM11

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Multiple Myeloma: 2010-2011

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