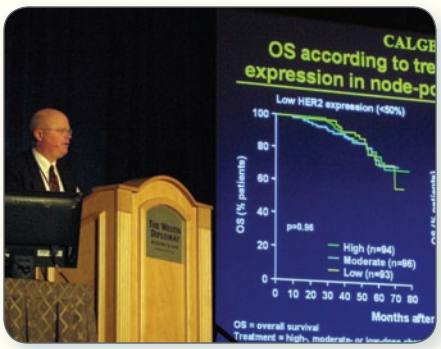
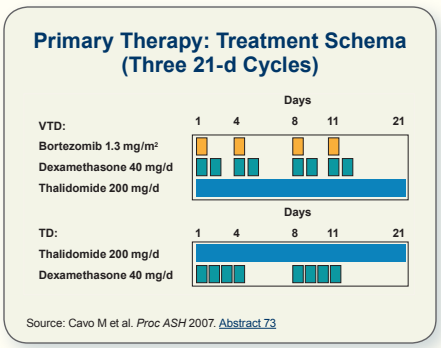
Year in Review

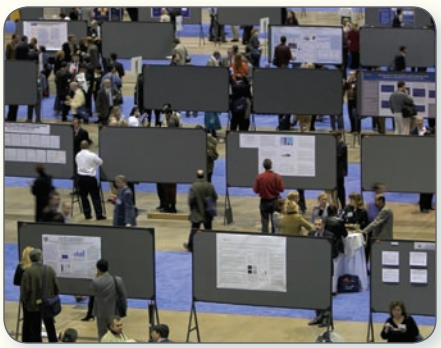
Multiple Myeloma: 2007-2008

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





Source: Cavo M et al. *Proc ASH* 2007. Abstract 73



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Monograph

CD with PowerPoint slide kit including expert commentary and case-based polling questions

FROM THE PUBLISHERS OF

Hematologic Oncology™ UPDATE

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Year in Review — Multiple Myeloma: 2007-2008
Continuing Medical Education (CME) Information

OVERVIEW OF ACTIVITY

Multiple myeloma (MM) accounted for 19,900 new cancer cases in the United States during 2007, with an estimated 10,790 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 utilizes the input of cancer experts and community physicians to frame a relevant discussion of recent research advances in myeloma that can be applied to routine clinical practice. This information will help medical oncologists, hematologists and hematology-oncology fellows formulate up-to-date clinical management strategies for patients.

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and changing practice standards in MM, and apply this information to clinical practice.
- Manage patients with MM considering recent advances related to front-line therapy, treatment of relapsed or refractory disease, maintenance and salvage therapy and autologous stem cell transplantation (ASCT).
- Develop a treatment plan for patients with MM who have compromised renal function.

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COMMERCIAL SUPPORT

This program is supported by an educational grant from Millennium Pharmaceuticals, The Takeda Oncology Company.

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COMMUNITY ONCOLOGIST PANEL

Drs Bobrow, Deutsch, Dresdner, Freedman, Glynn, Harwin, Hoffman, Levy, Lo, Merchant, Moriarty, Schnell, Schwartz and **Taylor** had no real or apparent conflicts of interest to disclose. The following physicians (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Bhardwaj — AC:** Celgene Corporation, Genentech BioOncology; **CA:** Novartis Pharmaceuticals Corporation; **Paid Research (PR):** Genentech BioOncology; **Stock Ownership (SO):** Celgene Corporation. **Dr Drullinsky — SB:** Novartis Pharmaceuticals Corporation. **Dr Farber — AC:** Biogen Idec, Genentech BioOncology; **SB:** Alexion Pharmaceuticals, Bayer Pharmaceuticals Corporation, Centocor Ortho Biotech Services. **Dr Gearhart — SB:** Eli Lilly and Company, Sanofi-Aventis. **Dr Hart — SB:** GlaxoSmithKline. **Dr Hussein — AC:** Bayer Pharmaceuticals Corporation, Roche Laboratories Inc; **SB:** Amgen Inc, Novartis Pharmaceuticals Corporation, Sanofi-Aventis. **Dr Moss — AC:** Celgene Corporation, Millennium Pharmaceuticals Inc, Pharmion Corporation; **PR:** Abraxis BioScience, Amgen Inc, Archimedes Development Limited, Eisai Inc, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Ortho Biotech Products LP, Pharmatech Inc, Sanofi-Aventis, Taiho Pharmaceutical Co Ltd. **Dr Pizzolato — AC:** Celgene Corporation; **SB:** ImClone Systems Incorporated, Sanofi-Aventis. **Dr Sabbath — AC:** Bristol-Myers Squibb Company; **SB:** Amgen Inc; **SO:** Amgen Inc, Celgene Corporation, GlaxoSmithKline, Novartis Pharmaceuticals Corporation. **Dr Seigel — SO:** AstraZeneca Pharmaceuticals LP, Celgene Corporation, Genentech BioOncology, Millennium Pharmaceuticals Inc. **Dr Vacirca — SB:** Abraxis BioScience, OSI Pharmaceuticals Inc, Sanofi-Aventis.

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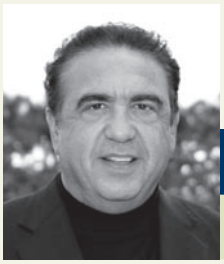

NEIL LOVE, MD

YEAR IN REVIEW

Charles M Farber, MD, PhD

Medical oncologists and hematologists face a continuous barrage of clinical research reports spanning a spectrum of different cancers. Our education group's committed content team of oncology clinicians knows this firsthand and spends its days and nights trying to stay on top of what's going on in more than two dozen tumor types. It's quite understandable that we spend a larger portion of that time focused on breast, colon and lung cancer — which make up at least two thirds of oncology practice — but in the last year alone we dove headfirst into the clinical and translational data in thyroid cancer, GIST, head and neck, ovary, renal cell, HCC and malignant glioma in order to produce in-depth education programs on these important topics.

Similarly, this slide set/monograph is our first major foray into multiple myeloma (MM). The need for effective CME in this unique cancer increased considerably after the recent data explosion at the December 2007 American Society of Hematology Annual Meeting, where no fewer than six Phase III randomized trials in MM were presented.

Realizing that this marked a true turning point in the management of this disease, we wanted to create a super-practical resource that clinicians could use to quickly yet effectively obtain the bottom line on what all this newly emerging research in MM really means to clinical practice.

FACULTY

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To do this, our clinical team identified more than 230 2007-08 MM abstracts, manuscripts, presentations and review articles from major publications such as *JCO*, the *New England Journal*, *Blood*, *The Lancet* and important scientific meetings including ASCO and ASH. We then enlisted the help of a stellar faculty of four highly knowledgeable myeloma mavens with superb teaching skills and an eye toward what's important. We asked them to take a look at our list and hone it down.

After several rounds of review, we arrived at a collection of 46 key publications, which we then sent to a select group of 23 practicing oncologists who agreed to consult with us on this project, including Dr Chuck Farber, a practicing doc who was previously on the faculty at Memorial Sloan-Kettering and worked closely with us as a gown-to-town liaison.

The community docs had previously worked with us on our *Meet The Professors* audio series, and we knew them to be highly knowledgable clinicians. They were given the important task of rating each article (on a 1-to-10 scale) for relevance and applicability to their practices. Based on the aggregated ratings, we eliminated the bottom half of the list, leaving us with 25 publications. We then posed two more challenges to these individuals:

1. **Segment the 25 papers into those that are essential for any oncologist or hematologist providing care to people with MM (Priority 1) and those that are important but not absolutely critical (Priority 2).**
2. **Provide three MM cases from their practices, along with relevant clinical questions they had about those cases. We asked that the cases reflect the most challenging decisions currently involving patients with this disease. Our content group — headed on this project by a progressively obsessed Rick Kaderman, PhD — studied and classified these decisions and used the most common questions as a further basis to evaluate the value of the 25 "contestants" for "pubs of the year."**

With both faculty and practicing doc input, we reached a consensus that the 11 papers/presentations referred to in Figure 1 were required understanding for any doc caring for a patient with MM. My informal vote for paper of the year is Cavo's stunning ASH presentation of a Phase III evaluation of VTD.

A close runner-up is Rajkumar's ECOG study on lenalidomide with high- and low-dose dex, followed by faculty member Paul Richardson's ASH data set on Rev/Vel/Dex. We then conducted in-depth interviews with the four faculty members about the papers and then combined their edited comments with supporting graphics to create the slides contained in this monograph.

Simultaneously, we analyzed all the submitted cases and from them developed 36 multiple-choice case scenarios that address the clinical questions that were most important to our community oncologist panel, and we asked our faculty to tell us how they would likely manage such a case currently. If it all sounds rather complex and nightmarish to implement, well....in a way, it was, except that the traffic cop for this electronic mayhem was our supremely talented faculty relations coordinator, Melissa Vives — an unflappable, profoundly organized human being who in a sweet, very gentle but highly insistent way, cannot be ignored when she asks for work returned on time.

When the dust settled, we had somehow been able to boil down one year's worth of clinical research in MM to approximately 137 data slides and 36 related case-based question slides that can be paired with keypad polling devices to facilitate interactive Q&A during live events. Our hope is that oncology clinicians will use this monograph and the PowerPoint slides contained on the enclosed CD for their own education or during lectures on this important subject. As in many areas of cancer medicine, biologic agents are revolutionizing clinical management of MM, and just in the past year, major research findings have had a clear-cut impact on treatment algorithms in practice.

We are hopeful that as more data emerge on an annual basis, we will be able to revisit this process to document for busy clinicians the most important developments in the field and provide an efficient review of the potential benefits of these advances to patients struggling with this disease.

— Neil Love, MD
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1 Process for Identifying Key Recent Reports on the Management of Multiple Myeloma

Initial Search* 1/2007 to 2/2008
(237 publications and meeting abstracts)

↓

Initial Faculty Review
(46 publications/abstracts selected)

↓

Community Oncologists' & Faculty Ratings (1-10 scale)

↓

Editorial Review of Ratings
(25 publications/abstracts selected)

↓

In-Depth Faculty Interviews

↙ ↘

11 essential publications/ presentations

14 recommended publications/ presentations

*** PubMed search of clinical trials, published in English between January 1, 2007 and February 30, 2008 (n = 103). Search of oral presentations from 2007 American Society of Hematology annual meeting (n = 87). Search of 2007 American Society of Clinical Oncology annual meeting (n = 47).**

2 Process for the Development of Clinical Case Scenarios and Polling Questions

Community Oncologists' Submission of Clinical Cases from Their Practices (Approximately 70 patients with multiple myeloma)

↓

Editorial Review of Cases for Key Clinical Questions

↓

Development of Prototype Clinical Case Scenarios and Poll Questions

↓

Editorial Review and Revision of Prototype Clinical Case Scenarios and Poll Questions (36 cases/questions)

↓

Faculty Submission of Responses to Cases

Bortezomib (Velcade®)-Thalidomide-Dexamethasone (VTD) versus Thalidomide-Dexamethasone (TD) in Preparation for Autologous Stem-Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (MM)

Cavo M et al, on behalf of the Italian Myeloma Network, GIMEMA, Italy.

American Society of Hematology 2007. Abstract 73

FACULTY COMMENTS

DR RICHARDSON: The GIMEMA trial compared induction with bortezomib/thalidomide/dexamethasone — the so-called VTD regimen — to thalidomide/dexamethasone (TD) in preparation for autologous transplantation. Impressive responses to primary therapy were seen, including a 36 percent nCR*/CR rate for VTD, versus nine percent for thal/dex, and a doubling in the number of patients achieving VGPR† or better with the addition of bortezomib to the thal/dex.

What was particularly interesting in my view was that although TD had a six percent rate of progressive disease, which is low, this was zero for VTD, suggesting that the combination of the three drugs was active in all the patients treated.

An important point observed in this trial was that bortezomib-based therapy was effective regardless of chromosome 13 deletion or other adverse risk features, including high $ß_2$-microglobulin and 4;14 translocation.

Whilst it's fair to say that we have been very pleased with the impact of bortezomib in the relapsed/refractory setting, the magnitude of impact in the up-front setting has now been found to be dramatic.

Thalidomide/dexamethasone has been a very important up-front combination. This study shows that when bortezomib is added to this combination, the quality and depth of responses are significantly improved, which is likely to translate into clinical benefit, although long-term follow-up data are of course needed and are awaited with interest.

DR JAKUBOWIAK: VTD was superior across the board compared to TD, and transplant did not nullify this difference, which means that it is important to initiate therapy with a superior regimen. At the end of transplant, you may have a higher percentage of patients achieving VGPR or CR, and the presumption is that this will eventually translate into a longer progression-free and overall survival.

* nCR = near complete response (CR, except immunofixation-positive)

† VGPR = very good partial response

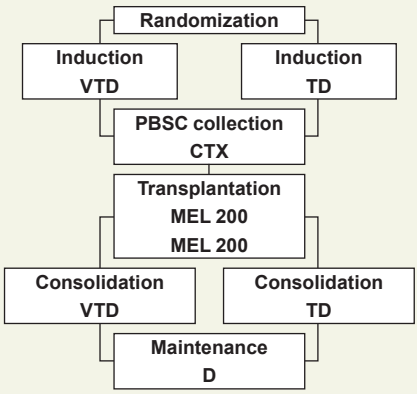
Background

- Phase I/II trial of VTD in 85 patients with refractory multiple myeloma (Pineda-Roman 2008):
  - Maximum tolerated dose: 1.3 mg/m^2 bortezomib and 150 mg thalidomide
  - Dose-limiting toxicity: Myelosuppression
  - PR rate 63%; nCR rate 22%
- Phase II trial of VTD in 38 patients with newly diagnosed multiple myeloma (Wang 2007):
  - Clinical response rate 87%; CR rate 16%

V = bortezomib; T = thalidomide; D = dexamethasone

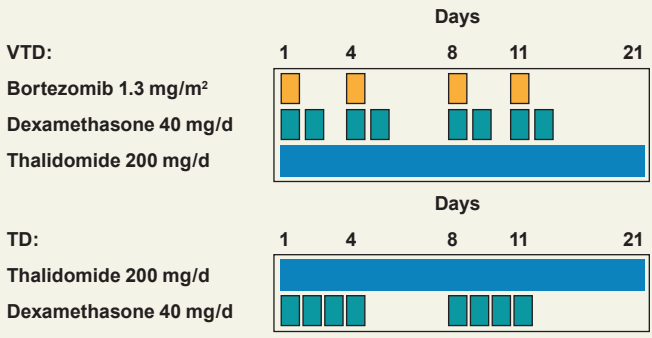
Source: Cavo M et al. *Proc ASH* 2007. Abstract 73

Study Design



Source: Cavo M et al. *Proc ASH* 2007. Abstract 73

Primary Therapy: Treatment Schema (Three 21-d Cycles)



Source: Cavo M et al. *Proc ASH* 2007. Abstract 73

Response to Primary Therapy

	VTD (n = 129)	TD (n = 127)	*p*-value
CR + nCR	36%	9%	<0.001
≥VGPR	60%	27%	<0.001
<PR	7%	20%	0.003
Progression	0%	5.5%	0.008

Source: Cavo M et al. *Proc ASH* 2007. Abstract 73

Key Grade III/IV Nonhematologic Adverse Events

	VTD (n = 129)	TD (n = 127)	*p*-value
Peripheral neuropathy	7%	2%	0.03
Skin rash	6.5%	1%	0.01
Deep vein thrombosis	3%	6.5%	0.01

Source: Cavo M et al. *Proc ASH* 2007. Abstract 73

Response to First ASCT

	VTD (n = 74)	TD (n = 79)	*p*-value
CR + nCR	57%	28%	<0.001
CR	45%	19%	<0.001
≥VGPR	77%	54%	0.003

Source: Cavo M et al. *Proc ASH* 2007. Abstract 73

Conclusions

- **VTD as primary therapy for multiple myeloma significantly increased the rate of CR + nCR (36%) or ≥VGPR (60%)**
- **Superior CR + nCR rate effected by VTD was not adversely influenced by t(4;14) or del(13)**
- **Grade III/IV adverse events, including SAE, were similar for VTD and TD, except for a higher rate of PN (7%) and rash (6.5%) with VTD, and of DVT (6.5%) with TD**
- **The relatively low toxicity profile of VTD was reflected by:**
  - **Low discontinuation rate of therapy (3%)**
  - **High probability (91%) of receiving >90% of planned bortezomib administrations**
  - **Absence of early deaths**

Source: Cavo M et al. *Proc ASH* 2007. Abstract 73

A Randomized Trial of Lenalidomide plus High-Dose Dexamethasone (RD) versus Lenalidomide plus Low-Dose Dexamethasone (Rd) in Newly Diagnosed Multiple Myeloma (E4A03)

Rajkumar SV et al.
American Society of Hematology 2007.
Abstract 74

FACULTY COMMENTS

DR RICHARDSON: ECOG-E4A03 is a landmark trial, which evaluated the activity and toxicity of high-dose dexamethasone versus lower-dose dexamethasone when combined with lenalidomide and how this affects patient outcome, including overall survival.

The most powerful message from this study was that the one-year Kaplan-Meier overall survival estimate is striking, with a 96.5 percent survival for lenalidomide and low-dose dexamethasone, which is probably the best seen in any Phase III trial of this size to date. In contrast, the high-dose arm did less well, with an 88 percent chance of one-year survival. Somewhat surprising was that the response rates were significantly higher for the high-dose dexamethasone arm, which ultimately performed poorer in terms of survival. Having said that, the overall response rates for both arms are very respectable, and I believe the good news for patients is that we're dealing with a new combination — lenalido-

Continued on page 11

Continued from page 10

mide and low-dose dex — which is associated with a very encouraging survival at one year, coupled with the convenience of an oral regimen. Unfortunately, high-dose dex contributes excess toxicity to this combination, and therefore, low-dose dex should generally be used. However, the quality of responses on low-dose dexamethasone was lower, and so this may indicate that we need a third drug, or even more, to achieve a better response and to potentially further enhance clinical benefit.

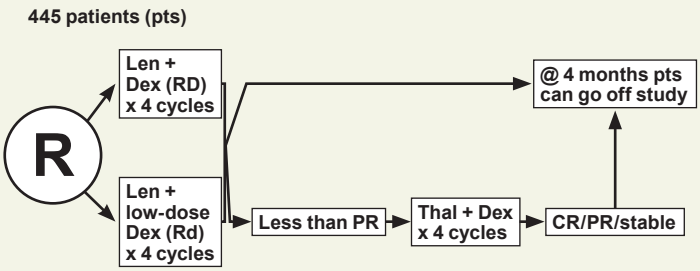
DR JAKUBOWIAK: Mostly, we eliminated the high toxicity levels with high-dose dex, which was the primary cause of early mortality, especially in older patients. It is important not to lose any patient from toxicity, but the switch to low-dose dex may haunt us. The response rate for Rd was clearly inferior compared to other active regimens, including PAD, VDD, RVD and VTD, which are in the 90 percent range. The response rate for Rd is approximately 70 percent. Some predict these patients will relapse earlier and have a shorter survival.

Background

- **Mayo Phase II trial (Rajkumar 2005; Lacy 2007) of Len/Dex as initial therapy for multiple myeloma (N = 34)**
  - **RR = 91%**
  - **CR/VGPR rate: 56%**
  - **88% OS at three years**

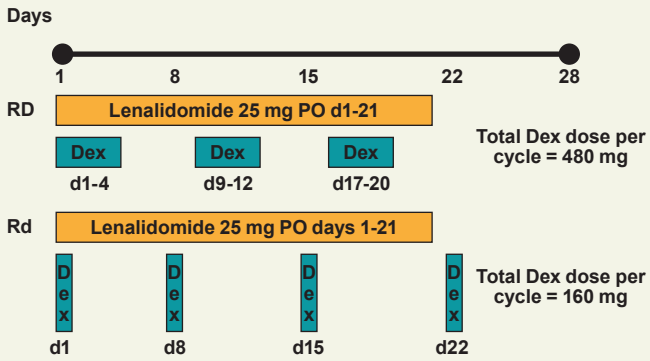
Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Study Design



Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Treatment Schedule



Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Best Overall Response

	RD (n = 196)		Rd (n = 190)	
CR	4%	52%*	2%	42%*
VGPR	48%		40%	
PR	30%		29%	

*CR + VGPR, *p*-value = 0.06

Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Response within Four Cycles

	RD (n = 196)		Rd (n = 190)	
CR	2%	82%*	1%	70%*
PR	80%		69%	

*CR + PR, *p*-value = 0.007

Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Survival Probability (95% CI)

	RD (n = 223)	Rd (n = 222)	*p*-value
12-month	0.88 (0.83-0.92)	0.96 (0.93-0.99)	0.003
24-month	0.75 (0.68-0.82)	0.87 (0.81-0.93)	0.009

Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Survival Rate by Age

	N	12-month survival probability (95% CI)	24-month survival probability (95% CI)
Age < 65			
Len-high dex	104	0.92 (0.87-0.97)	0.85 (0.78-0.93)
Len-low dex	108	0.97 (0.94-1.00)	0.91 (0.84-0.98)
		$p = 0.13$	$p = 0.16$
Age ≥ 65			
Len-high dex	119	0.84 (0.77-0.91)	0.67 (0.56-0.77)
Len-low dex	114	0.95 (0.84-1.00)	0.82 (0.74-0.91)
		$p = 0.01$	$p = 0.009$

Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Serious Adverse Events (≥Grade III): Nonhematologic

	RD (n = 222)	Rd (n = 219)	Fisher exact *p*-value
DVT/PE	25%	9%	<0.001
Infection/pneumonia	14%	7%	0.030
Nonneuropathic weakness	10%	4%	0.008
Any nonhematologic toxicity (Grade ≥ III)	65%	45%	<0.001
Early deaths (<4 months)	5%	0.5%	0.01

Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Serious Adverse Events (≥Grade III): Hematologic

	RD (n = 222)	Rd (n = 219)	Fisher exact *p*-value
Hemoglobin	8.1%	6.8%	0.718
Platelets	5.4%	5.5%	1.000
Neutrophils	11.7%	18.7%	0.047

Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Cause of Death

(Median follow-up: 21 months)

	RD N = 46	Rd N = 25
	N	N
Progressive disease	26	17
Thromboembolism	5	1
Infection	4	3
Cardiac	6	2
Stroke	1	1
Respiratory failure	1	0
Second cancer	1	0
Unknown	2	1

Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Conclusions

- **RD and Rd are highly active in newly diagnosed multiple myeloma (MM)**
- **Rd had lower response rates, but this was within the 15% limit that was defined in study design as clinically equivalent**
- **Rd is associated with superior OS**
- **Response duration, TTP or PFS with Rd not inferior**
- **The excess mortality in the RD arm was due to both disease progression (myeloma deaths) and increased toxicity**
- **This study has major implications for the use of high-dose dexamethasone in the treatment of newly diagnosed MM**

Source: Rajkumar SV et al. *Proc ASH* 2007. Abstract 74

Lenalidomide, Bortezomib, and Dexamethasone (Rev/Vel/Dex) as Front-Line Therapy for Patients with Multiple Myeloma (MM): Preliminary Results of a Phase 1/2 Study

Richardson P et al.
American Society of Hematology 2007.
Abstract 187

FACULTY COMMENTS

DR RICHARDSON: Our Phase I/II study combined bortezomib with the lenalidomide/dexamethasone couplet in the up-front setting.

We had preclinical data to suggest that the triplet was at least additive and possibly synergistic. Clinical experience in the relapsed/refractory setting demonstrated that this drug regimen was active, even in patients in whom either bortezomib or lenalidomide had failed.

We identified a maximally tolerated dose in the up-front setting of 1.3 mg/m^2 of bortezomib, 25 milligrams of lenalidomide and dexamethasone at 20 milligrams, administered according to the protocol schedule. This translated into a 98 percent overall response rate using EBMT criteria, with 100 percent of patients treated at the maximum planned dose achieving PR or better.

We also observed low rates of deep vein thrombosis and peripheral neuropathy, and generally the toxicity profile of the combination proved manageable.

The regimen is already moving into a Phase III clinical trial through ECOG, led by my colleague Dr Rafael Fonseca, in which Rev/Vel/Dex is compared to bortezomib and dexamethasone. Also, Brian Durie from SWOG is testing Rev/Vel/Dex versus lenalidomide and low-dose dexamethasone. Participation in these clinical trials is especially encouraged, and other studies using the Rev/Vel/Dex platform are also underway.

DR LONIAL: Many of us believe now that Rev/Vel/Dex is probably the backbone on which we're going to start adding other drugs to build a CHOP-like regimen for myeloma.

DR ORLOWSKI: In the future, Rev/Vel/Dex may prove to be the best regimen for all patients.

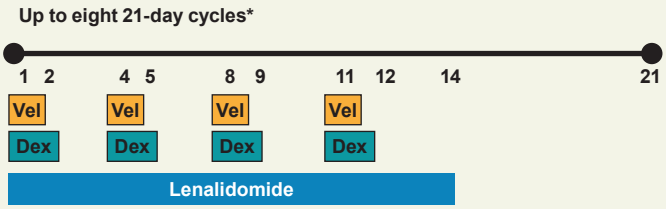
Being able to achieve response rates of close to 100 percent with shorter durations of therapy is encouraging.

Background

- Phase I: Lenalidomide/bortezomib with or without dexamethasone in relapsed/refractory MM: 58% response rate
- Phase II study of Rev/Vel/Dex in relapsed/refractory MM (Richardson 2007b)
  - 73% overall response rate — including 55% CR/nCR/PR
  - Well tolerated but Dex dose lowered

Source: Richardson P et al. *Proc ASH* 2007. Abstract 187

Study Design



* Dex, amended to 20 mg/10 mg for cycles 1-4/5-8 based on safety data

- Patients ≥PR may proceed to ASCT after ≥4 cycles
- Maintenance therapy permitted in patients ≥SD using weekly (days 1 and 8) schedule of Vel, and Dex on days 1, 2, 8 and 9
- Antithrombotic therapy with daily aspirin (81 or 325 mg)
- Antiviral therapy as herpes zoster prophylaxis

Source: Richardson P et al. *Proc ASH* 2007. Abstract 187

Efficacy — Overall

- Best response (EBMT/UC) in 42 evaluable patients
  - 9 CR (21%)
  - 3 nCR (7%)
  - 29 PR (69%)
    - 10 VGPR (24%)
  - 1 MR (2%)
- Overall response rate; CR/nCR + PR: 98% (95% CI: 87.4% to 99.9%)
- CR/nCR + VGPR: 52%
- CR/nCR: 29%

Source: Richardson P et al. *Proc ASH* 2007. Abstract 187

Conclusions

- Rev/Vel/Dex is active and well tolerated in patients with newly diagnosed MM
  - ORR currently 98% in 42 evaluable patients (Phase I/II), including 52% CR/nCR/VGPR
  - Maximum planned dose has been reached: Vel 1.3 mg/m^2, Rev 25 mg, Dex 20 mg
- Toxicities are manageable
  - No GIII/IV PNY and only 2 DVTs
- Rev/Vel/Dex has not adversely affected stem cell harvesting in most patients; transplant course unremarkable to date

Source: Richardson P et al. *Proc ASH* 2007. Abstract 187

Future Directions

- Additional analyses are under way for
  - Cytogenetics
  - Proteomics
  - Gene expression profiling
- Future directions:
  - Rev/Vel/Dex versus Rev/low-dose dex (SWOG)
  - Rev/Vel/Dex versus Vel/low-dose dex (ECOG)
  - Rev/Vel/Dex versus cyclophosphamide/Rev/Vel/Dex (Phase I/II)
- Rev/Vel/Dex with other novel agents (Phase I/II)

Source: Richardson P et al. *Proc ASH* 2007. Abstract 187

Bortezomib Appears to Overcome the Poor Prognosis Conferred by Chromosome 13 Deletion in Phase 2 and 3 Trials

Jagannath S et al.
Leukemia 2007;21(1):151-7.

FACULTY COMMENTS

DR ORLOWSKI: This paper reported on a retrospective analysis of the impact of bortezomib on the poor prognosis conferred by chromosome 13 deletion.

They examined data from the Phase II SUMMIT trial, which led to the first approval of bortezomib for third-line or later therapy, and the APEX trial, which led to approval of bortezomib for use in the second line or later. They showed that bortezomib seemed to overcome the adverse effects of the deletion of chromosome 13.

The APEX trial data are particularly nice in that regard because this trial had the control group with dexamethasone on one arm. The patients on that arm with deletion of chromosome 13 did more poorly than those without, as would be expected.

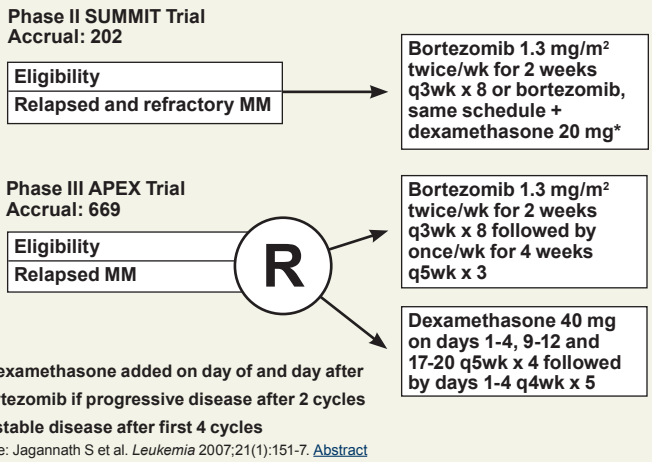
In the bortezomib arm, however, the patients with this deletion fared about the same as patients who did not have deletion of chromosome 13.

Background

- **Chromosome 13 deletion (del[13]) is associated with poor prognosis in multiple myeloma (MM), independent of therapy**
  - **Chemotherapy OS 10 versus 35 months (Seong 1998)**
  - **Chemotherapy with single or tandem autotransplantation (Desikan 2000; Tricot 1997)**
  - **Miniallogeneic transplantation (Kröger 2004)**

Source: Jagannath S et al. *Leukemia* 2007;21(1):151-7. Abstract

SUMMIT and APEX Trials



*** Dexamethasone added on day of and day after bortezomib if progressive disease after 2 cycles or stable disease after first 4 cycles**

Source: Jagannath S et al. *Leukemia* 2007;21(1):151-7. Abstract

SUMMIT Trial: Impact of Del(13) on Efficacy of Bortezomib

	Chromosome 13 deletion by metaphase cytogenetics		
	Present	Absent	*p*-value
Unmatched analysis			
n (percent)	26 (18%)	121 (82%)	—
Response rate	24%	33%	NS
Median overall survival	10 months	15 months	NS
Matched-pair analysis*			
n	26	26	—
Response rate	24%	38%	NS
Median overall survival	10 months	NR	NS

NS = not significant; NR = not reached

***Balanced for patient age and International Staging System (ISS)**

Source: Jagannath S et al. *Leukemia* 2007;21(1):151-7. Abstract

APEX Trial: Impact of Del(13) on Response and Survival

	Bortezomib			Dexamethasone		
	Del(13) by metaphase cytogenetics			Del(13) by metaphase cytogenetics		
	Present	Absent	*p*-value	Present	Absent	*p*-value
Unmatched analysis						
n (percent)	11 (15%)	63 (85%)	—	13 (14%)	81 (86%)	—
Response rate	20%	38%	NS	8%	19%	NS
Median OS	12.5 months	NR	0.0379	8.3 months	NR	0.0073
Matched-pair analysis*						
n	9	17	—	12	24	—
Response rate	25%	35%	NS	9%	26%	NS
Median OS	12.5 months	NR	NS	3.3 months	NR	0.002

NS = not significant; NR = not reached; *Balanced for patient age, adverse prognostic variables and ISS parameters

Source: Jagannath S et al. *Leukemia* 2007;21(1):151-7. Abstract

Conclusions

- **In SUMMIT and APEX, patients with del(13) by metaphase cytogenetics appear to have a poorer prognosis**
  - **The difference was not significant in SUMMIT**
  - **The difference was more pronounced in the dexamethasone arm of APEX**
- **Matched-pair analyses indicate that bortezomib may overcome some of the adverse prognostic impact of del(13)**
- **Sample size in this study was small. Further studies are required to confirm these findings**

Source: Jagannath S et al. *Leukemia* 2007;21(1):151-7. Abstract

Activity and Safety of Bortezomib in Multiple Myeloma Patients with Advanced Renal Failure: A Multicenter Retrospective Study

Chanan-Khan AA et al.
Blood 2007;109(6):2604-6.

FACULTY COMMENTS

DR LONIAL: The Chanan-Khan paper was a multicenter, retrospective analysis evaluating the ability to use bortezomib in patients with hemodialysis-dependent renal failure.

It reassures us that the response rates are good. The toxicity associated with bortezomib in the setting of hemodialysis was not worse than one would have expected in a similarly heavily pretreated patient population.

Bortezomib is probably one of the first drugs you want to use in patients with renal dysfunction. If the renal dysfunction is related to myeloma, you have a good chance of reversing it.

DR JAKUBOWIAK: This study puts a stamp on what we already know — namely, we don't have to be worried about renal insufficiency for patients who will be treated with bortezomib-based regimens. The response rates and toxicities are in the same range, regardless of renal functioning.

Background

- **30% of patients with newly diagnosed multiple myeloma (MM) have renal dysfunction**
- **1-13% have renal failure requiring dialysis support**
- **Renal dysfunction:**
  - **Is associated with shorter survival or early death**
  - **Poses challenges in the delivery of effective and safe treatment**
  - **Does not seem to negatively affect response rates, toxicity or treatment discontinuation in patients with relapsed and/or refractory MM receiving bortezomib**

Source: Chanan-Khan AA et al. *Blood* 2007;109(6):2604-6. Abstract

Patients and Methods

- Retrospective review of consecutive patients from 4 US institutions experienced in the treatment of MM
- Treatment with bortezomib alone or in combination with other agents
- Renal failure requiring dialysis at the time of bortezomib treatment
- Demographics, treatment schedule, response by EBMT criteria and adverse events collected from patient records

Source: Chanan-Khan AA et al. *Blood* 2007;109(6):2604-6. Abstract

Results

- 24 patients treated with bortezomib between May 2003 and November 2005
- 83% received bortezomib at starting dose of 1.3 mg/m^2 in combination with other agents (median number of cycles = 5)
- Four out of 18 patients with available data became independent of dialysis

Overall response rate (n = 20 for patients with response data)	75%
Complete response	25%
Near complete response	5%
Partial response	45%
Median duration of response	12.5+ months

Source: Chanan-Khan AA et al. *Blood* 2007;109(6):2604-6. Abstract

Conclusions

- Overall response rate and durability of response are comparable to MM patients with primarily normal renal function treated in the relapsed setting
- 83% of patients received treatment after completion of dialysis, suggesting that delivery of bortezomib subsequent to dialysis does not affect its activity
- Bortezomib has a potentially positive impact on renal function, with normalization occurring in some patients

Source: Chanan-Khan AA et al. *Blood* 2007;109(6):2604-6. Abstract

Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma

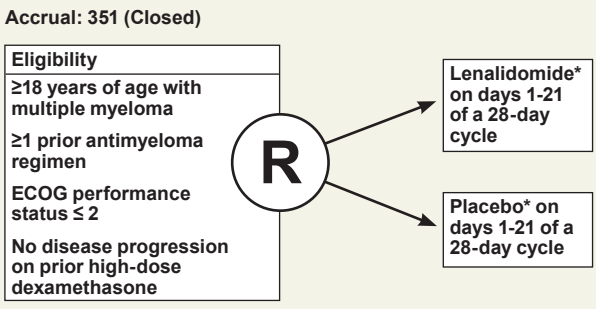
Dimopoulos M et al, on behalf of the Multiple Myeloma (010) Study Investigators.
N Engl J Med 2007;357(21):2123-32.

FACULTY COMMENTS

DR ORLOWSKI: This paper reports on one of the two studies that led to the combination of lenalidomide and dexamethasone becoming a standard approach for relapsed or refractory multiple myeloma. Comparing the combination to dexamethasone alone, the median time to progression was approximately 11 months as opposed to less than five months, respectively, and the median overall survival had not yet been reached for the combination but was approximately 20.6 months for dexamethasone alone.

Thromboembolic events were more common with the combination, and I believe most people in the field would recommend prophylactic anticoagulants, although debate with regard to the specific strategy continues. The International Myeloma Working Group published a consensus paper in *Leukemia*, with Antonio Palumbo as the lead author, which says every patient who receives lenalidomide and low-dose dexamethasone should take a baby aspirin daily, at the minimum.

Study Design



*All patients received oral dexamethasone 40 mg/d on days 1-4, 9-12 and 17-20 for the first 4 cycles, then on days 1-4 only.

Source: Dimopoulos M et al. *N Engl J Med* 2007;357(21):2123-32. Abstract

Efficacy Results

	L + D (n = 176)	D (n = 175)	Hazard ratio*	*p*-value
Median TTP (months)	11.3	4.7	2.85	<0.001
Median OS (months)	Not yet reached	20.6	0.66†	0.03
Overall response	60.2%	24.0%	—	<0.001
CR	15.9%	3.4%		<0.001
Near CR	8.5%	1.7%		
PR	35.8%	18.9%		

***HR > 1 favors L + D; † Hazard ratio for death; L = lenalidomide; D = dexamethasone**

Source: Dimopoulos M et al. *N Engl J Med* 2007;357(21):2123-32. Abstract

Select Grade III/IV Adverse Events

	Lenalidomide + dexamethasone (n = 176)	Dexamethasone (n = 175)
Febrile neutropenia	3.4%	0%
Neutropenia	29.5%	2.3%
Thrombocytopenia	11.4%	5.7%
Infection	11.3%	6.2%
Deep vein thrombosis*	4.0%	3.5%
Venous thromboembolism*	11.4%	4.6%
Pulmonary embolism*	4.5%	1.2%
Fatigue	6.8%	3.4%

***Thromboprophylaxis was not required**

Source: Dimopoulos M et al. *N Engl J Med* 2007;357(21):2123-32. Abstract

Conclusions

- **L combined with D is more effective than D alone in patients with relapsed or refractory MM**
  - **Increased TTP, CR rate, overall response rate and OS**
- **Primary toxicity associated with lenalidomide/dexamethasone is hematologic, which is manageable with dose adjustments**
- **Thromboembolic complications are more common with lenalidomide/dexamethasone**
- **Lenalidomide is not associated with peripheral neuropathy**

Source: Dimopoulos M et al. *N Engl J Med* 2007;357(21):2123-32. Abstract

Lenalidomide plus Dexamethasone for Relapsed Multiple Myeloma in North America

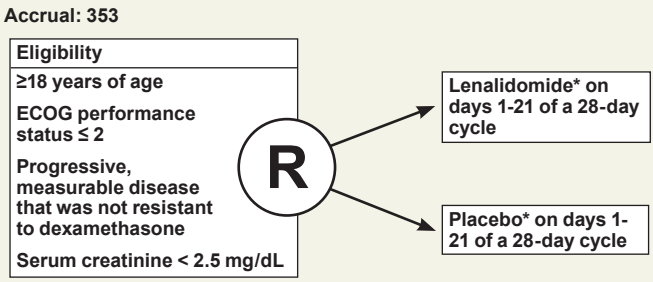
Weber DM et al, on behalf of the Multiple Myeloma (009) Study Investigators. *N Engl J Med* 2007;357(21):2133-42.

FACULTY COMMENTS

DR JAKUBOWIAK: This study shows that the combination of lenalidomide (R) and dexamethasone (D) in patients who had relapsed is superior across the board to the prior traditional standard therapy, which was dexamethasone. RD was highly superior to D for progression-free and overall survival. So this is another study showing that more patients can be rescued successfully from relapsing disease, and as a result more will have their lives prolonged.

DR LONIAL: This was one of the trials used to obtain FDA approval for lenalidomide/dexamethasone in patients with relapsed myeloma. An improvement was seen not only in response rate but also in overall and progression-free survival. Toxicities associated with RD were manageable, and the incidence of DVT was relatively low. This is an important study, as it clearly establishes the response rate and efficacy of RD in relapsed myeloma.

Study Design



*All patients received oral dexamethasone 40 mg/d on days 1-4, 9-12 and 17-20 for the first 4 cycles, then on days 1-4 only.

Source: Weber D et al. *N Engl J Med* 2007;357(21):2133-42. Abstract

Results

	LD (n = 177)	D (n = 176)	Hazard ratio
Median TTP	11.1 months	4.7 months	0.35*
Median OS	29.6 months	20.2 months	0.44*
Overall response CR Near CR PR	61.0% 14.1% 10.2% 36.7%	19.9%* 0.6%* 1.1%* 18.2%	—

*** $p < 0.001$**

L = lenalidomide; D = dexamethasone

Source: Weber D et al. *N Engl J Med* 2007;357(21):2133-42. Abstract

Select Grade III and IV Adverse Events

	LD (n = 177)	D (n = 175)	*p*-value
Neutropenia	41.2%	4.5%	$p < 0.001$
Anemia	13.0%	5.1%	—
Thrombocytopenia	14.7%	6.9%	$p = 0.02$
Any infection	21.4%	12.0%	$p = 0.14$
Pneumonia	12.4%	7.4%	—

Source: Weber D et al. *N Engl J Med* 2007;357(21):2133-42. Abstract

Select Grade III and IV Adverse Events

	LD (n = 177)	D (n = 175)	*p*-value
Deep vein thrombosis*	11.9%	3.4%	—
Venous thromboembolism*	14.7%	3.5%	$p < 0.001$
Pulmonary embolism*	3.4%	0.6%	—
Hyperglycemia	10.8%	8.6%	—
Fatigue	6.2%	6.3%	—
Peripheral neuropathy	1.7%	1.1%	—

*** Thromboprophylaxis was not required**

Source: Weber D et al. *N Engl J Med* 2007;357(21):2133-42. Abstract

Conclusions

- **LD is superior to D in patients with relapsed or refractory MM**
  - **Overall response rate (61% versus 20%)**
  - **Median time to progression (11.1 months versus 4.7 months)**
  - **Median overall survival (29.6 months versus 20.2 months)**
- **Neutropenia is more common with LD than D**
  - **Managed with dose adjustment, G-CSF or both**
- **Thromboembolic events are more common with LD than D**
  - **Managed with anticoagulants**

Source: Weber D et al. *N Engl J Med* 2007;357(21):2133-42. Abstract

Randomized Phase III Study of Pegylated Liposomal Doxorubicin plus Bortezomib Compared with Bortezomib Alone in Relapsed or Refractory Multiple Myeloma: Combination Therapy Improves Time to Progression

Orlowski RZ et al, on behalf of
DOXIL-MMY-3001 Study Investigators.
J Clin Oncol 2007;25(25):3892-901.

FACULTY COMMENTS

DR ORLOWSKI: Our Phase III trial compared bortezomib with or without pegylated liposomal doxorubicin (PLD) in patients with relapsed or refractory multiple myeloma.

The median time to progression, progression-free survival and 15-month survival rate are all significantly greater with the combination.

The overall response rate doesn't appear much different between the two arms, partially because we have to report it in an intent-to-treat analysis as opposed to the response-evaluable population. Still, the response quality, as measured by CR and very good PR (VGPR), was about 30 percent with bortezomib and PLD versus 20 percent with bortezomib alone.

Also, we saw that there seemed to be a special benefit with this combination for patients with high-risk features, such as patients with both relapsed and refractory disease or patients with a

Continued on page 27

Continued from page 26

moderate to high ß$_2$-microglobulin. Usually, trials show just the opposite — that it's the good-risk patients that do the best. I can't speculate as to why we saw this opposite effect.

DR LONIAL: This paper clearly established that while the overall response rate was not appreciably different, a much higher rate of VGPR or better was observed in the patients treated with PLD and bortezomib. This led to an improvement in time to progression and overall survival.

I believe this is a two-drug combination that improves overall survival compared to single-agent bortezomib. Based on this trial, you can feel confident that PLD with bortezomib will have a better response rate for a bortezomib-naïve patient.

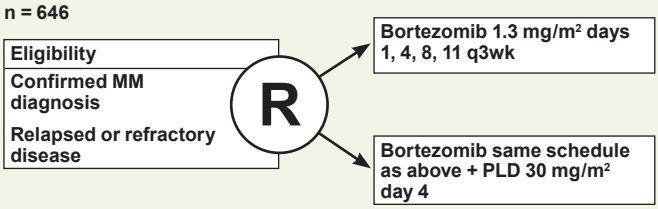
DR JAKUBOWIAK: To Dr Orlowski's credit, this was the first randomized study in patients with relapsed disease to show that a two-drug combination with a novel agent was superior to a novel single agent, which was bortezomib.

Background

- **Phase I (bortezomib + pegylated liposomal doxorubicin [PLD]) demonstrated safety and efficacy (Orlowski 2005)**
  - **CR = 36%**
  - **Overall RR = 73%**
  - **TTP = 9.3 months**
  - **Median overall survival > 3 years**

Source: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-901. Abstract

Study Design



Primary endpoint: Time to progression

MM = multiple myeloma; PLD = pegylated liposomal doxorubicin

Source: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-901. Abstract

Initial Analysis (7.2 Months)

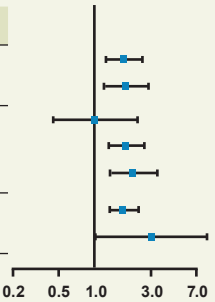
Efficacy	Bortezomib + PLD (n = 324)	Bortezomib (n = 322)	Hazard ratio	*p*-value
Median TTP	9.3mo	6.5mo	1.82	0.000004
Median PFS	9.0mo	6.5mo	1.69	0.000026
15-month survival	76%	65%	—	0.03
Overall response rate (CR + PR)	44%	41%	—	0.43
CR + VGPR	27%	19%	—	0.0157
Median DOR	10.2mo	7.0mo	—	0.0008

TTP = time to progression; PFS = progression-free survival;
CR = complete response; PR = partial response; DOR = duration of response

Source: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-901. Abstract

Hazard Ratio Estimates for Time to Disease Progression

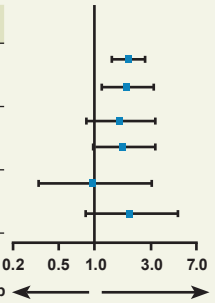
Subgroup		N	HR	95% CI
Age (years)	<65	396	1.75	1.26 to 2.45
	≥65	250	1.82	1.19 to 2.79
$ß_2$-microglobulin (mg/L)	≤2.5	90	1.02	0.45 to 2.29
	>2.5 to ≤5.5	359	1.83	1.3 to 2.58
	>5.5	197	2.11	1.36 to 3.28
Response to prior treatment	Yes	590	1.75	1.35 to 2.29
	No	56	2.99	1.05 to 8.54



Source: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-901. Abstract

Hazard Ratio Estimates for Time to Disease Progression

Subgroup		N	HR	95% CI
Prior anthracycline use	Yes	436	1.88	1.38 to 2.55
	No	210	1.83	1.12 to 3
Cytogenetic abnormality	Yes	117	1.62	0.83 to 3.18
	No	141	1.71	0.95 to 3.08
Chromosome 13 deletion	Yes	47	0.94	0.32 to 2.76
	No	70	1.89	0.78 to 4.58



Source: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-901. Abstract

Select Grade III/IV Adverse Events (AE)

	Bortezomib + PLD (n = 318)	Bortezomib (n = 318)	*p*-value
Any AE Grade III/IV	80%	64%	<0.001
Peripheral neuropathy	4%	9%	NR
Neutropenia	29%	15%	<0.001
Febrile neutropenia	3%	2%	NR
Thrombocytopenia	23%	16%	0.249
Bleeding/hemorrhage	4%	1%	NR
Thromboembolic events	1%	1%	NR
Diarrhea	7%	4%	0.034
Hand-foot syndrome	5%	0%	<0.001
Cardiac events	2%	3%	NR

NR = not reported

Source: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-901. Abstract

Select Adverse Events (%)

	PLD + bortezomib (n = 318)		Bortezomib (n = 318)	
	Total	Grade III/IV	Total	Grade III/IV
Peripheral neuropathy	35	4	39	9
Febrile neutropenia	3	3	2	2
Bleeding/hemorrhage	14	4	9	1
Thromboembolic events	1	1	1	1
Cardiac events	10	2	7	3
Alopecia	2	NA	1	NA

Source: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-3901. Abstract

Symptomatic Cardiac Adverse Events (AE)

	PLD + bortezomib (n = 318)		Bortezomib (n = 318)	
Cardiac AE	Total %	Treatment-related* %	Total %	Treatment-related* %
Total patients with AE	7	—	5	—
Congestive heart failure	3	2	3	1
Symptomatic arrhythmia	3	2	1	1
Coronary ischemia disease	1	1	1	0
Other	2	2	1	1

*** Rated by investigator as at least probably related to treatment**

Source: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-901. Abstract

PLD with Bortezomib versus Bortezomib: Conclusions

- **PLD/bortezomib is superior to bortezomib in relapsed/refractory MM**
  - **Significantly prolonged DOR, PFS and TTP**
  - **Evidence of benefit in patients with moderate to high ß$_2$-microglobulin**
  - **Early evidence of survival benefit**
- **PLD/bortezomib resulted in more Grade III/IV AEs**
  - **No increase in febrile neutropenia**
  - **No increase in treatment-emergent neuropathy**
- **PLD/bortezomib represents a new therapeutic option for relapsed/refractory MM**

Source: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-3901. Abstract

MMY-3002: A Phase 3 Study Comparing Bortezomib-Melphalan-Prednisone (VMP) with Melphalan-Prednisone (MP) in Newly Diagnosed Multiple Myeloma

San Miguel JF et al, on behalf of
the MMY-3002 study investigators.
American Society of Hematology 2007. Abstract 76

FACULTY COMMENTS

DR RICHARDSON: It was exciting to see Dr San Miguel present the randomized Phase III VISTA trial at the 2007 ASH meeting.

A protocol-specified interim analysis showed that the combination with bortezomib and melphalan/prednisone was significantly superior to melphalan/prednisone alone for all of the efficacy endpoints, including time to progression, progression-free survival, overall survival and time to next therapy.

The difference in complete response rate — 35 percent for the bortezomib-based arm versus five percent for the control arm — was striking.

CR rates of this order of magnitude for older patients who are not candidates for transplant are quite remarkable, in my opinion.

Continued on page 31

Continued from page 30

We at Dana-Farber were the lead enroller for the US, and our experience was that the responses to the combination were rapid and deep. Moreover, adverse cytogenetics and poor renal function had no impact on VMP efficacy overall.

In terms of the side-effect profile, cytopenias were seen in both arms, and the neuropathy rate was higher, as one would expect, with VMP. In the majority of cases, however, it was reversible using the dose-reduction algorithm that is now a standard with bortezomib-based therapy.

Interestingly, low rates of deep vein thrombosis were observed on both arms with this combination approach.

The clinical implication of these data is that bortezomib and melphalan/prednisone is now an important standard in the up-front setting for patients who are not candidates for high-dose therapy.

Background

Phase I/II trial (Mateos 2006): VMP in newly diagnosed MM (median age = 75) resulted in:

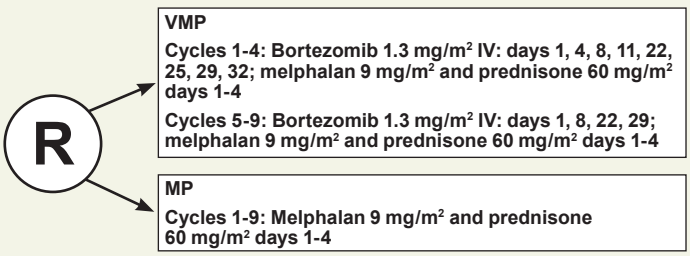
- **CR rate = 32%**
- **CR/nCR rate = 43%**
- **Projected 2-year survival = 86%**
- **Median time to progression not yet reached at 16-month follow-up**

V = bortezomib; M = melphalan; P = prednisone; MM = multiple myeloma

Source: San Miguel JF et al. *Proc ASH* 2007. Abstract 76

Eligibility and Design

- **Symptomatic MM, end organ damage with measurable disease**
  - **≥65y or <65y and not transplant eligible; KPS ≥ 60%**



9 x 6-week cycles (54 weeks) in both arms

Source: San Miguel JF et al. *Proc ASH* 2007. Abstract 76

Patient Demographics and Disease Characteristics

	VMP, N = 344	MP, N = 338
Male	51%	49%
White	88%	87%
Median age, years Age ≥ 75y	71 31%	71 30%
KPS ≤ 70%	35%	33%
ISS Stage I/II/III	19/47/35%	19/47/34%
$ß_2$-m <2.5/2.5-5.5/>5.5 mg/L (median $ß_2$-m, mg/L)	12/55/33% (4.2)	12/55/33% (4.3)
Albumin < 3.5 g/dL, (median albumin, g/dL)	58% (3.3)	59% (3.3)

Source: San Miguel JF et al. *Proc ASH* 2007. Abstract 76

Patient Demographics and Disease Characteristics (continued)

	VMP, N = 344	MP, N = 338
Region: Europe/N America/other	78/9/12%	78/9/13%
IgG/IgA/light chain	64/24/8%	62/26/8%
Lytic bone lesions	65%	66%
Plasma cells in bone marrow biopsy, median	40%	41%
Serum creatinine, median (mg/dL) CrCl ≤30/>30-60/>60 ml/min	1.1 6/48/46%	1.1 5/50/46%
History of neurological conditions	18%	20%
History of cardiac conditions	35%	31%

Source: San Miguel JF et al. *Proc ASH* 2007. Abstract 76

Results

- **682 patients randomly assigned from 12/04 to 9/06**
- **VMP was significantly superior for all efficacy endpoints**
- **IDMC recommended that the study stop in 9/07**

Efficacy endpoint	HR	*p*-value
TTP	0.540	0.000002
PFS	0.609	0.00001
OS	0.607	0.00782
TNT	0.522	0.000009
CR	11.2*	<0.000001

***Odds ratio**

Source: San Miguel JF et al. *Proc ASH* 2007. Abstract 76

VISTA Response Data

	EBMT criteria		
	VMP (n = 344)	MP (n = 338)	*p*-value
ORR (CR + PR)	69%	34%	10^{-10}
CR	30%	4%	—
PR	40%	30%	—

Sources: San Miguel JF et al. *Proc ASH* 2007. Abstract 76; Velcade Prescribing Information, June 2008.

VISTA Efficacy

	VMP (n = 344)	MP (n = 338)	Hazard ratio	*p*-value
Time to progression	24.0mo	16.6mo	0.483	<0.000001
52% reduced risk of progression on VMP				
Overall survival	NR	NR	0.607	0.0078
Two-year	82.6%	69.5%		
Age < 75y	84.0%	74.0%		
Age ≥ 75y	79.0%	60.0%		
40% reduced risk of death on VMP				
Treatment-related deaths	1%	2%	—	—

NR = not yet reached

Source: San Miguel JF et al. *Proc ASH* 2007. Abstract 76

Grade III and IV Adverse Events (%)

VMP serious adverse events: 46%; MP: 36%

	VMP (n = 340)		MP (n = 337)	
	Grade III	Grade IV	Grade III	Grade IV
Neutropenia	30	10	23	15
Thrombocytopenia	20	17	16	14
Anemia	16	3	20	8
Gastrointestinal symptoms	19	1	5	<1
Peripheral sensory neuropathy	13	<1	0	0
Fatigue	7	1	2	0
Asthenia	6	<1	3	0
Pneumonia	5	2	4	1
Herpes zoster	3	0	2	0

Source: San Miguel JF et al. *Proc ASH* 2007. Abstract 76

Grade III and IV Adverse Events (%)

- Transfusion (26% versus 35%) and EPO support (34% versus 42%) were somewhat lower on the VMP arm
- PN resolved or improved in 75% of cases in a median of 64 days
- DVT rate was low and the same on both arms (1%)

Source: San Miguel JF et al. *Proc ASH* 2007. Abstract 76

Conclusions

- VMP was superior to MP for all efficacy endpoints, including TTP, PFS, OS, time to next treatment and response rate
- VMP was well tolerated
  - Patients remained on therapy for a median of 46 weeks (8 cycles) versus 39 weeks with MP (7 cycles)
  - VMP was associated with more Grade III/IV peripheral neuropathy and fatigue than MP
- Adverse cytogenetics, age and renal function had no effect on VMP efficacy

Source: San Miguel JF et al. *Proc ASH* 2007. Abstract 76

VELCADE®/Dexamethasone (Vel/D) versus VAD as Induction Treatment Prior to Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (MM): Updated Results of the IFM 2005/01 Trial

Harousseau JL et al.
American Society of Hematology 2007. Abstract 450

FACULTY COMMENTS

DR RICHARDSON: The IFM 2005/01 trial is another landmark study with an innovative design comparing bortezomib and dexamethasone versus the standard approach of VAD as an induction treatment prior to at least one transplant.

It examined the role of consolidation chemotherapy as a part of induction and evaluated the need for tandem transplants based on the quality of response to each induction approach.

The results of response to induction were presented at the recent ASH 2007 meeting and showed a pretransplant VGPR or better of 47 percent with bortezomib and dexamethasone, versus 19 percent with VAD.

A key message from this trial is that the depth and quality of response were not only better pretransplant but also continued post-transplant.

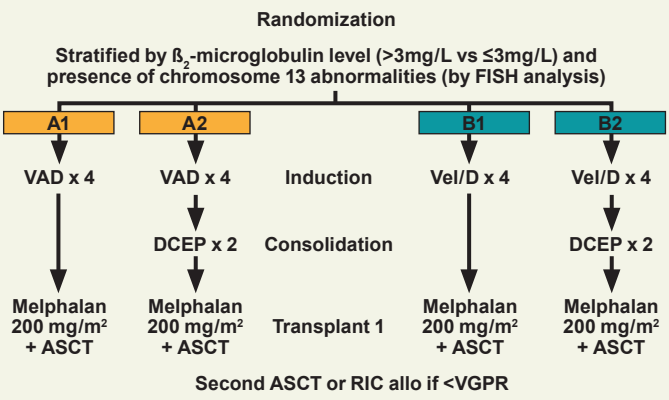
Importantly, this randomized trial suggested that consolidation chemotherapy with DCEP did not convey benefit.

In aggregate, the data suggest that bortezomib-based therapy pretransplant should be considered a new standard, because it is generally believed that the quality of response pretransplant matters, and bortezomib-based therapy also appears to enhance the quality of response post-transplant.

DR JAKUBOWIAK: The study demonstrated superior response rates for bortezomib and dexamethasone compared to VAD, regardless of whether the patient had poor-risk cytogenetics and that superiority was maintained when patients subsequently underwent transplant.

Harousseau and colleagues designed this study so that patients who achieved a VGPR after first transplant did not need to receive a second transplant. So, fewer patients treated with bortezomib and dexamethasone needed to undergo a second transplant. This could save lives because there is a five percent mortality rate with any single transplant.

Study Design



Source: Harousseau JL et al. *Proc ASH* 2007. Abstract 450

Response to Induction*

	VAD (n = 242)	Vel/D (n = 240)	*p*-value
CR	2.9%	9.6%	0.0023
CR + nCR	8.3%	21.3%	<0.0001
≥VGPR	18.6%	46.7%	<0.0001
≥PR	62.8%	80.0%	<0.0001

***Intent to treat; investigator assessment**

Source: Harousseau JL et al. *Proc ASH* 2007. Abstract 450

Post-ASCT Response*

	VAD (n = 242)	Vel/D (n = 240)	*p*-value
CR + nCR	23.6%	35.0%	0.0056
≥VGPR	41.7%	61.7%	<0.0001
≥PR	72.7%	80.4%	0.0463

***Intent to treat**

Source: Harousseau JL et al. *Proc ASH* 2007. Abstract 450

Impact of ß$_2$-M and Del(13) on Post-Induction Responses (CR + nCR)

	VAD	Vel/D	*p*-value
ß$_2$-m level			
>3.0 mg/L	7.9% (n = 140)	18.3% (n = 137)	0.0101
≤3.0 mg/L	8.8% (n = 102)	25.2% (n = 103)	0.0018
Chr 13			
Deletion	9.6% (n = 104)	25.7% (n = 101)	0.0024
Normal/NE	7.3% (n = 138)	18.0% (n = 139)	0.0071

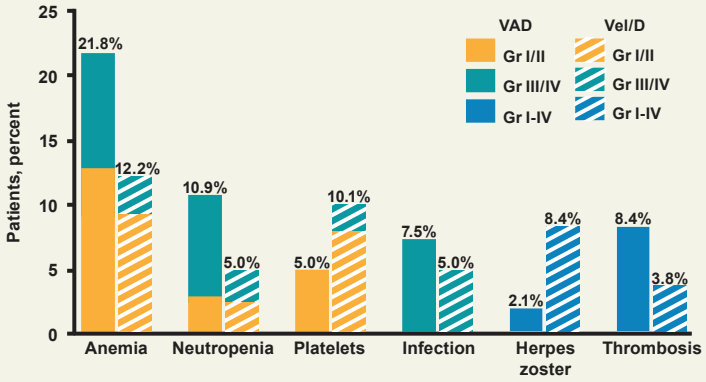
Source: Harousseau JL et al. *Proc ASH* 2007. Abstract 450

Impact of DCEP Consolidation ITT Analysis

	No DCEP A1 + B1 N = 242	DCEP A2 + B2 N = 240	*p*-value
CR + nCR	16.5%	19.2%	0.41
≥VGPR	33.5%	37.5%	0.30
≥PR	71.1%	71.3%	0.93
NE	3.7%	15.4%	—

Source: Harousseau JL et al. *Proc ASH* 2007. Abstract 450

Hematologic Toxicity



Source: Harousseau JL et al. *Proc ASH* 2007. Abstract 450

Nonhematologic Toxicities (All Grades)

	VAD (n = 239)	Vel/D (n = 238)
Fatigue	16.7%	21.4%
Rash	5.4%	10.1%
Gastrointestinal symptoms	25.9%	22.3%
Peripheral neuropathy	22.6%	35.3%

Source: Harousseau JL et al. *Proc ASH* 2007. Abstract 450

Conclusions

- **Vel/D was well tolerated and significantly improved the postinduction response rate**
- **DCEP consolidation did not significantly improve outcome**
- **Better response after induction translated to better response after ASCT**

Source: Harousseau JL et al. *Proc ASH* 2007. Abstract 450

Melphalan and Prednisone plus Thalidomide versus Melphalan and Prednisone Alone or Reduced-Intensity Autologous Stem Cell Transplantation in Elderly Patients with Multiple Myeloma (IFM 99-06): A Randomised Trial

Facon T et al, on behalf of the Intergroupe Francophone du Myélome (IFM).
Lancet 2007;370:1209-18.

FACULTY COMMENTS

DR ORLOWSKI: The bottom line of this paper is that with MPT we see about an 18-month improvement in median overall survival over MP.

I would conclude that if you have a patient who is not eligible for transplant and who has a reasonably good performance status and organ function, he or she should receive either MPT or MPV because those are the most active regimens, although they are associated with an increased risk of toxicity.

With MPT in particular, the patient can have problems with thrombosis and infection, while other issues like cytopenias are less problematic or at least easier for the average hematology/oncology practitioner to deal with. I believe that the current best combinations we have to offer are MPT, based on this paper and Hulin's data, and MPV, based on the San Miguel paper.

Continued on page 39

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DR LONIAL: MPT clearly was the winner across the board in terms of overall survival, progression-free survival and response rate. A little more myelosuppression, somnolence and peripheral neuropathy were observed with MPT compared to MP alone. The deep vein thrombosis rate was a little higher than I would have expected, but they didn't use any prophylaxis. I believe this was the trial that established MPT as a standard for elderly patients with myeloma who are not transplant eligible.

DR JAKUBOWIAK: The simple answer from the Facon study is that the addition of thalidomide to MP results in a superior response rate, progression-free survival and overall survival compared to MP alone. Secondly, there is no way to "rescue" this superiority by using reduced-intensity ASCT, with melphalan 100 mg/m^2, in elderly patients. Those patients did not fare better than those treated with MP. So, to some extent, this tells us that adding a new drug to a regimen is better than escalating traditional cytotoxic drugs.

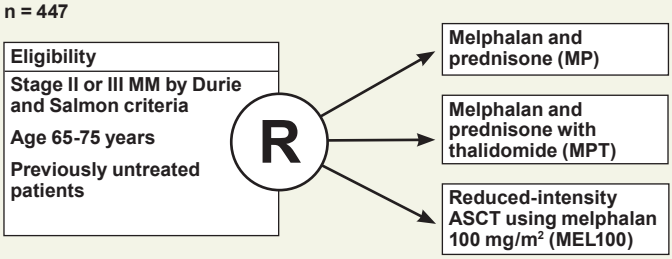
Background

- **In newly diagnosed multiple myeloma, melphalan and prednisone with thalidomide (MPT) improves response rate (RR) and event-free survival (EFS) but with increased toxicity and no evident survival benefit (Palumbo 2006)**
- **High-dose M followed by autologous stem cell transplantation (ASCT) is not tolerated by most elderly patients (Attal 2003; Child 2003)**
- **GIMEMA trial of M 100 mg/m^2 (Palumbo 2004) → ASCT versus standard MP in patients 50 to 70 years old**
  - **Improved RR, EFS and OS**

Source: Facon T et al. *Lancet* 2007;370:1209-18. Abstract

Eligibility and Design

n = 447



Primary endpoint: Overall survival (OS)

Secondary endpoints: Best response rate, progression-free survival (PFS), survival after progression, toxicity

Source: Facon T et al. *Lancet* 2007;370:1209-18. Abstract

Efficacy (51.5-Month Follow-Up)

				HR, *p*-value	
	MP (n = 196)	MEL100 (n = 126)	MPT (n = 125)	MPT vs MP	MPT vs MEL100
Median OS	33.2mo	38.3mo	51.6mo	0.59, 0.0006	0.59, 0.027
Median PFS	17.8mo	19.4mo	27.5mo	0.51, <0.0001	0.59, 0.0002
Survival after progression	11.4mo	14.1mo	13.4mo	Not reported	Not reported
Response					
At least PR	35%	65%	76%	<0.0001	—
At least VGPR	7%	43%	47%	<0.0001	—
CR	2%	18%	13%	0.0008	—

(39 to 43% of patients were 70 years old or older.)

Source: Facon T et al. *Lancet* 2007;370:1209-18. Abstract

Grade III/IV Toxicities

	MP (n = 193)	MEL100 (n = 122)	MPT (n = 124)
Anemia	14%	100%	14%
Neutropenia	26%	100%	48%
Thrombocytopenia	10%	100%	14%
Severe hemorrhage	1.5%	3%	0
Infection	9%	49%	13%
Thrombosis or embolism	4%	8%	12%
Peripheral neuropathy	0	0	6%
Cardiac symptoms	0.5%	10%	2%
Nausea	1%	7%	1%
Somnolence/fatigue/dizziness	0%	0%	8%
Any Grade III/IV nonhematologic toxicity	16%	58%	42%

Source: Facon T et al. *Lancet* 2007;370:1209-18. Abstract

Conclusions

- **MPT compared to MP**
  - **Significantly increased RR, PFS and OS**
  - **More frequent hematologic and nonhematologic toxicity**
- **MPT compared to MEL100**
  - **RR similar, but increased PFS and OS**
  - **Less frequent hematologic and nonhematologic toxicity**
- **High incidence of relapse after MEL100 → ASCT**

Source: Facon T et al. *Lancet* 2007;370:1209-18. Abstract

Prospective, Randomized Study of Single Compared with Double Autologous Stem-Cell Transplantation for Multiple Myeloma: Bologna 96 Clinical Study

Cavo M et al, on behalf of the
Bologna 96 Clinical Study Group.
J Clin Oncol 2007;25(17):2434-41.

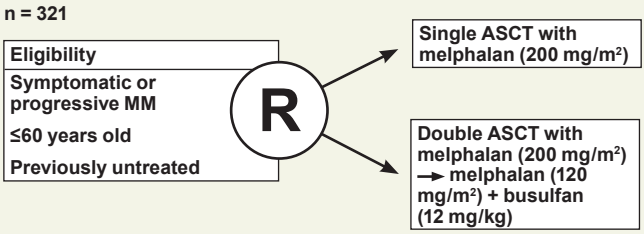
FACULTY COMMENTS

DR LONIAL: A number of trials have evaluated single versus tandem transplant, and few have been positive. The French trial was the only other positive trial for tandem transplant versus single transplant with melphalan, and it demonstrated that patients who had achieved a VGPR or better did not benefit from a second transplant. So I believe many of us have adopted that same approach. Patients who achieve a VGPR or better don't need a second cycle of high-dose therapy and transplant.

The Cavo trial showed that tandem transplant appeared to be superior to single transplant in terms of event-free survival and response rate. No real difference in seven-year overall survival was observed, but a difference at five years favoring double autologous transplant was seen.

My conclusion is that, for patients who fail to achieve a near CR — and in the French trial, a VGPR — a tandem transplant is of benefit.

Design



Source: Cavo M et al. *J Clin Oncol* 2007;25(17):2434-41. Abstract

Results

Patients who failed to achieve at least an nCR after one transplantation

	Single ASCT n = 94	Double ASCT n = 66	*p*-value
Median relapse-free survival	22 months	46 months	<0.001
Median event-free survival	22 months	42 months	<0.001
Seven-year overall survival rate	47%	60%	0.10

Source: Cavo M et al. *J Clin Oncol* 2007;25(17):2434-41. Abstract

Toxicity

Most frequent WHO Grade III/IV nonhematologic toxicities	Single ASCT n = 130	Double ASCT n = 99
Mucositis	25%	28%
Infections	21%	24%
Transplant-related mortality	3%	4%

Source: Cavo M et al. *J Clin Oncol* 2007;25(17):2434-41. Abstract

Superiority of Lenalidomide (Len) plus High-Dose Dexamethasone (HD) Compared to HD Alone as Treatment of Newly-Diagnosed Multiple Myeloma (NDMM): Results of the Randomized, Double-Blinded, Placebo-Controlled SWOG-S0232

Zonder JA et al.
American Society of Hematology 2007. Abstract 77

FACULTY COMMENTS

DR LONIAL: SWOG-S0232 — the sister trial of ECOG-E4A03 — compared lenalidomide/high-dose dexamethasone (len/HD) to dexamethasone alone (HD) for the treatment of newly diagnosed myeloma.

It was a placebo-controlled Phase III trial, which was interrupted after enrollment of the first 25 or 30 patients because of a high incidence of deep vein thrombosis before prophylaxis was mandated. It was stopped early at 198 patients because of the E4A03 data — which I believe was somewhat premature — suggesting that it was unethical to use len/HD. So it's not a truly finished trial in terms of accrual to its real power.

In this study, we saw the real CR rate of 22 percent for len/HD in the up-front setting. What I think is intriguing about this trial — and the follow-up is short — is that the 12-month overall survival was 93 percent, which is much better than the 12-month survival rate for len/HD in ECOG-E4A03.

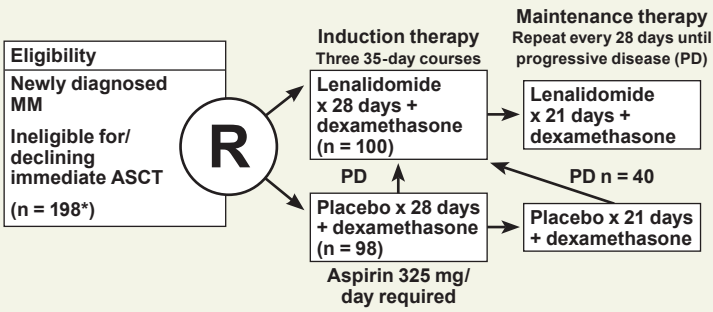
The advantage of the SWOG trial is that it is easier to evaluate because it has a true control arm, and its data are consistent with what we have seen with len/dex in other trials.

The risk of infection was higher in the len/dex arm, but these were predominately Grade I/II, and neutropenia can be seen with lenalidomide. Thrombosis was the big surprise from this trial, and aspirin did not appear to reduce the risk. Practically speaking, len/dex has essentially replaced thal/dex because of the ECOG and SWOG data.

I believe that the responses are encouraging, but I also believe that we can do even better with combinations. Hence, RVD has become our standard, but I think len/HD or VD are reasonable up-front induction regimens.

DR JAKUBOWIAK: This presentation had the potential to be an important study, but it addressed a question that was already answered in the Weber and Dimopoulos studies, albeit not in a front-line setting, which demonstrated that lenalidomide/dexamethasone was superior to dexamethasone alone.

Design



***Protocol closed after early interim analysis by DSMC.**

Source: Zonder JA et al. *Proc ASH* 2007. Abstract 77

Efficacy Results

	Lenalidomide + high-dose dexamethasone (n = 78)		High-dose dexamethasone alone (n = 85)		*p*-value
CR	22%	}84%	4%	}53%	0.001
PR	62%		49%		
12-month PFS	77%		55%		0.002
12-month OS	93%		91%		NS

Source: Zonder JA et al. *Proc ASH* 2007. Abstract 77

Select Adverse Events

	Lenalidomide + high-dose dexamethasone (n = 78)	High-dose dexamethasone alone (n = 85)	*p*-value
Infections (Grade I-V)	51.4%	28%	0.003
Neutropenia (Grade III/IV)	13.8%	2.4%	0.010
Thrombotic events	(25) 32.1%	(7) 8.2%	0.089

Source: Zonder JA et al. *Proc ASH* 2007. Abstract 77

The Effect of Induction Therapy with Novel Agents on Stem Cell Mobilization in Multiple Myeloma

Amitabha Mazumder et al.
Proc ASCO 2007. Abstract 8102

FACULTY COMMENTS

DR JAKUBOWIAK: The Mazumder study demonstrates what was separately reported by the Mayo Clinic — namely, the IMiDs® seem to reduce the number of stem cells prior to transplant, thus increasing the number of phereses required.

When we use initial regimens that include thalidomide or lenalidomide, we must be cautious not to extend the induction therapy because we may have difficulty collecting enough stem cells.

Bortezomib-based regimens have less impact on stem cell collection. In the context of our current treatment algorithm, which incorporates transplant and potentially tandem transplant, collecting enough stem cells for tandem transplant is clinically important.

On average, most studies will have seven to nine million stem cells collected, which is barely enough for one stem cell transplant, much less a tandem transplant. If you reduce the number of stem cells collected, you may end up not being able to deliver two transplants for patients who may have indication for a second transplant.

My operational adjustment is that I'm more careful not to extend the initial period with patients who are on a thalidomide-based regimen or a lenalidomide-based regimen, and I try to mobilize them earlier than I would normally.

With a bortezomib-based regimen, I don't have to be that concerned because I know that if I am seeing a continuous response to therapy, for instance, I keep going until I reach plateau, so I have less contamination of collections with myeloma cells and there is improvement in some outcomes. Some people agree that that's important. Others who are not sure whether they will go for transplant anticipate that the patient may receive treatment longer, and they will wait to see whether the patient's performance status improves.

In that setting I would likely favor a bortezomib-based rather than a thalidomide-based regimen because I could give the patient's performance status more time to recover, so he or she could be a more acceptable candidate for transplant.

Methods

- **Retrospective, single-center evaluation of stem cell mobilization after induction therapy (IT) with either thalidomide/dexamethasone (TD; n = 22) or bortezomib/dexamethasone (VD; n = 18)**
- **All patients balanced: Initial Durie-Salmon stage, median number of cycles of IT, response to IT, bone marrow cellularity and involvement and time from end of therapy to collection**
- **All patients mobilized with G-CSF 10 mcg/kg and collected in large volume pheresis, with a goal of at least 6 x 10^6 CD34+ cells/kg for tandem transplant**

Source: Mazumder A et al. *Proc ASCO* 2007. Abstract 8102

Results

	TD (n = 22)	VD (n = 18)	*p*-value
Number of patients requiring ≥4 days of collection*	6	1	<0.01
Number of patients requiring ≥3 pheresis*†	17	4	<0.005
Number of patients collecting enough CD34+ on day 1	1	4	<0.01
Number of CD34+ cells collected	183 x 10^6 in 65 phereses = 2.8 x 10^6	213 x 10^6 in 41 phereses = 5.2 x 10^6	<0.005
Days to ANC > 500/mcl (range)	11 (10-18)	11 (10-15)	>0.2
Days to platelets > 20,000/mcl (range)	16 (14-22)	15 (14-18)	<0.05

*** To reach goal of 6 x 10^6 CD34+ cells/kg; † 4/4 patients who had received lenalidomide (L) required ≥3 phereses.**

Source: Mazumder A et al. *Proc ASCO* 2007. Abstract 8102

Conclusions

- **Yield of stem cells with V > T**
  - **V < T (and L?) in number of phereses required**
  - **V > T in number of CD34+ cells per pheresis**
- **A one-day delay in engraftment was evident for T versus V**
- **Lower yields may be clinically important when attempting to obtain stem cells from the elderly, patients with prior radiation therapy or patients with higher bone marrow plasma cell infiltration.**
- **IMiDs may act differently, biologically, than V on the bone marrow.**

Source: Mazumder A et al. *Proc ASCO* 2007. Abstract 8102

Consolidation with Bortezomib, Thalidomide and Dexamethasone Induces Molecular Remissions in Autografted Multiple Myeloma Patients

Ladetto M et al, on behalf of the Italian Multiple Myeloma Network, GIMEMA. American Society of Hematology 2007. Abstract 530

FACULTY COMMENTS

DR LONIAL: This trial evaluated VTD as consolidation therapy after an autologous transplant. They showed nicely that they were able to achieve molecular complete remissions (CRs) in about a quarter of the patients, which is something that has not been studied before. It's a small study with encouraging data. In and of itself, however, I believe it's food for thought more than anything else.

Personally, the way I'm starting to think about novel agents versus transplant is that a transplant can only take you so low in terms of minimal residual disease. I believe the new drugs can probably help you achieve a lower level of minimal residual disease. This trial certainly proves that point because melphalan alone wasn't enough to get most of these patients to a molecular CR. They required VTD.

My questions are, did they even need the transplant? Could you do this with bortezomib and thalidomide or bortezomib and lenalidomide as induction?

Study Design

Accrual: 40 (Closed)

Eligibility
CR or VGPR after ASCT
No prior bortezomib or thalidomide
IgH rearrangement present

→ **Consolidation therapy: VTD [bortezomib + thalidomide + dexamethasone] x 4**

Molecular monitoring at study entry, after 2 VTD courses, end of treatment and then every 6 months

Source: Ladetto M et al. ASH 2007. Abstract 530

VTD Consolidation After ASCT: Response Rates

Response	Response at study entry (n = 39)	Response after consolidation therapy (n = 27)
CR, %	23	66
nCR, %	13	15
VGPR, %	64	15
PD, %	0	4

Source: Ladetto M et al. ASH 2007. Abstract 530

Melphalan-Prednisone-Thalidomide (MP-T) Demonstrates a Significant Survival Advantage in Elderly Patients ≥ 75 Years with Multiple Myeloma Compared with Melphalan-Prednisone (MP) in a Randomized, Double-Blind, Placebo-Controlled Trial, IFM 01/01

Hulin C et al, on behalf of the Intergroupe Francophone du Myelome (IFM). American Society of Hematology 2007. Abstract 75

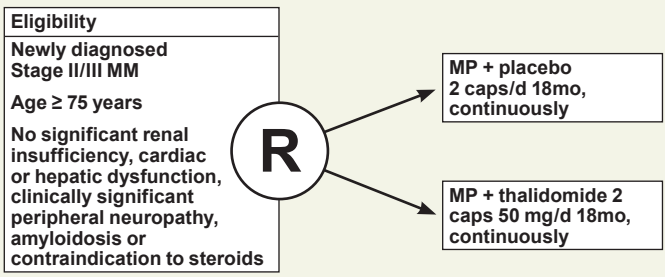
FACULTY COMMENTS

DR ORLOWSKI: In the Hulin study, they examined a truly nontransplant-eligible population — patients age 75 or older — and showed major advantages for MP-T, even in this older patient population. The overall survival was 45 months with MP-T versus approximately 28 months with MP. I believe anytime we can increase overall survival by 18 months or so, that's a dramatic benefit.

They also collected data about the efficacy of the next therapy these patients received after progression. Most of the patients on the MP arm received thalidomide, whereas patients on the MP-T arm received a variety of therapies, some with more thalidomide, some with bortezomib.

In both groups the median survival after relapse was approximately nine months. That tells me that what we do second line is less important than what we do first line and suggests that we need to go with our best therapy up front.

Trial Design



- All patients received 12 cycles of MP every 6 weeks
  - Melphalan 0.2 mg/kg/d days 1-4
  - Prednisone 2 mg/kg/d days 1-4
- Clodronate administered to all patients
- No anticoagulant prophylaxis was planned

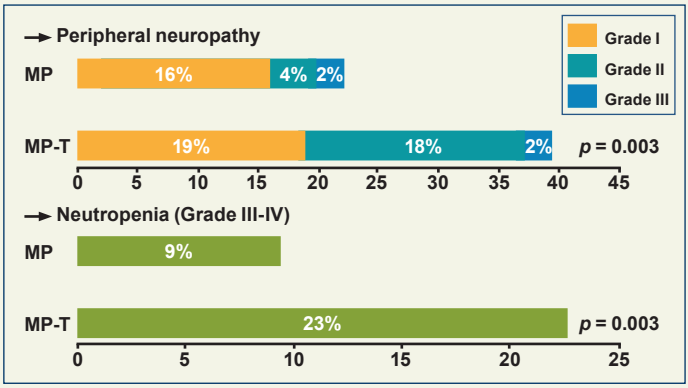
Source: Hulin C et al. *Proc ASH* 2007. Abstract 75

Efficacy (Intent to Treat)

	MP-T (n = 113)	MP (n = 116)	*p*-value
OS	45.3 months	27.7 months	0.033
PFS	24.1 months	19.0 months	0.001
TTP	27.0 months	20.9 months	0.0009

Source: Hulin C et al. *Proc ASH* 2007. Abstract 75

Toxicity*



*** Toxicity significantly different between MP-T and MP**

Source: Hulin C et al. *Proc ASH* 2007. Abstract 75

Safety and Efficacy of Bortezomib in High-Risk and Elderly Patients with Relapsed Multiple Myeloma

Richardson PG et al. *British Journal of Haematology* 2007;137(5):429-35.

FACULTY COMMENTS

DR ORLOWSKI: This paper examined the safety and efficacy of bortezomib in patients who were at high risk and elderly patients with relapsed disease. Indeed, older age by itself is a high-risk feature in patients with multiple myeloma.

The findings show that for advanced ISS stage, patients age 65 or older and patients with more than one prior line of therapy, bortezomib continued to be superior to dexamethasone. The data here are similar to those for the overall APEX population.

DR LONIAL: In this subset analysis of the APEX trial, the response rate for bortezomib in older patients with relapsed disease was clearly as good as for younger patients. Among patients who had received more than one prior line of therapy, the response rate held up with 34 percent achieving a CR and PR. I believe these are more confirmatory data.

Outcomes in Patients Over Age 65

	Bortezomib (n = 125)*	High-dose dexamethasone (n = 120)†
CR + PR	40%	18%[1]
Median TTP	5.5 months	4.3 months[2]
One-year survival	79%	63%[3]

*** n = 116 for CR + PR; † n = 115 for CR + PR; [1] $p = 0.0004$; [2] $p = 0.002$; [3] $p = 0.009$**

Source: Richardson PG et al. *Br J Haem* 2007;137(5):429-35. Abstract

Outcomes in Patients Who Received >One Prior Line of Therapy

	Bortezomib (n = 200)*	High-dose dexamethasone (n = 217)†
CR + PR	34%	13%[1]
Median TTP	4.9 months	2.9 months[1]
One-year survival	75%	62%[2]

*** n = 187 for CR + PR; † n = 202 for CR + PR; [1] $p < 0.0001$; [2] $p = 0.004$**

Source: Richardson PG et al. *Br J Haem* 2007;137(5):429-35. Abstract

Outcomes in Patients with MM Refractory to Last Prior Line of Therapy

	Bortezomib (n = 212)*	High-dose dexamethasone (n = 219)†
CR + PR	35%	13%[1]
Median TTP	5.5 months	2.8 months[1]
One-year survival	74%	63%[2]

*** n = 199 for CR + PR; † n = 202 for CR + PR; [1] *p* = <0.0001; [2] *p* = 0.01**

Source: Richardson PG et al. *Br J Haem* 2007;137(5):429-35. Abstract

Efficacy and Safety of Bortezomib in Patients with Renal Impairment: Results from the APEX Phase 3 Study

San-Miguel JF et al.
Leukemia 2008;22(4):842-9.

FACULTY COMMENTS

DR JAKUBOWIAK: The San-Miguel paper published in *Leukemia* is a subset analysis from the APEX study. The conclusions are similar to the Chanan-Khan paper, although this is from a randomized, Phase III study.

Essentially, this analysis indicates that bortezomib is active and well tolerated in patients with different degrees of renal insufficiency. No differences in toxicity or efficacy were seen, regardless of degree of renal failure, which was a key observation.

DR LONIAL: This is an important paper because it clearly establishes the efficacy of bortezomib in patients with renal dysfunction. These data suggest that it's safe to use bortezomib without dose modification in patients with low creatinine clearances. For patients with hepatic dysfunction, I would be more cautious. However, we use bortezomib in patients with renal failure at full doses all the time. Bortezomib reverses it in a fair number of patients.

Efficacy of Bortezomib in Patients with and without Renal Impairment

	Bortezomib				High-dose dexamethasone			
	Renal impairment*				Renal impairment*			
	None	Mild	Mod	Sev	None	Mild	Mod	Sev
CR + PR (n)	36% (118)	40% (137)	37% (43)	47% (15)	11% (123)	25% (118)	17% (52)	10% (10)
Median TTP months, (n)	6.3 (127)	6.2 (141)	5.6 (45)	4.2 (17)	2.8 (133)	4.9 (122)	2.9 (57)	2.1 (11)
Median OS months, (n)	NE (127)	30.0 (141)	22.8 (45)	22.0 (17)	29.1 (133)	24.3 (122)	12.6 (57)	17.4 (11)

NE = not estimable; CCr = creatinine clearance

*** None (CCr > 80 mL/min); mild (CCr 51-80 mL/min); moderate (CCr 30-50 mL/min); severe (CCr < 30 mL/min)**

Source: San-Miguel JF et al. *Leukemia* 2008;22(4):842-9. Abstract

Extended Follow-Up of a Phase 3 Trial in Relapsed Multiple Myeloma: Final Time-To-Event Results of the APEX Trial

Richardson PG et al.
Blood 2007;110(10):3557-60.

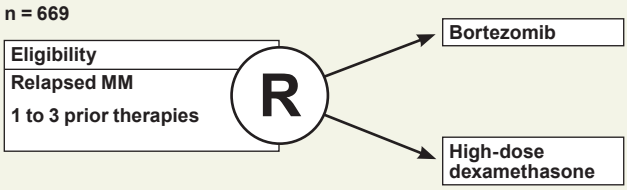
FACULTY COMMENTS

DR LONIAL: This was an updated analysis of the APEX trial, and we learned that the response rate with bortezomib increased. This paper shows that with longer follow-up, the responses we saw in APEX held up and were durable. This is further confirmation of the data we had from the original paper.

The other piece of information I would take away from this paper is that patients on APEX were treated for a total of eight cycles, unless they achieved a CR, in which case they were treated for two cycles beyond CR. I believe the key is to treat them to maximal benefit, which in this trial was eight cycles.

DR ORLOWSKI: Richardson's extended follow-up of the APEX trial — comparing bortezomib versus high-dose dexamethasone in patients with relapsed multiple myeloma — provides us with longer follow-up. With a median follow-up of 22 months, we see the response rate with bortezomib increases from the previously reported 38 percent to 43 percent.

APEX Trial Design*



*Assessment of Proteasome Inhibition for Extending Remissions

Source: Richardson PG et al. *Blood* 2007;110(10):3557-60. Abstract

Efficacy Results: Median Follow-Up 22 Months

	Bortezomib[1] (n = 333)		High-dose dexamethasone[2] (n = 336)		Hazard ratio, *p*-value
Complete response	9%	}43%	<1%	}18%	NA, <0.001
Partial response	34%		17%		
Median TTP	6.2 months		3.5 months		NA, $p < 0.001$
Median OS*	29.8 months		23.7 months		0.77, $p = 0.027$
One-year* survival	80%		67%		NA, $p = 0.001$

*Survival analysis based on >62% of the patients receiving dexamethasone crossing over to bortezomib; NA = not available; [1]Updated analysis; [2]Initial analysis, arm halted

Source: Richardson PG et al. *Blood* 2007;110(10):3557-60. Abstract

Incorporating Bortezomib into Up-Front Treatment for Multiple Myeloma: Early Results of Total Therapy 3

Barlogie B et al. *British Journal of Haematology* 2007;138(2):176-85.

FACULTY COMMENTS

DR JAKUBOWIAK: Barlogie and colleagues from Little Rock believe that post-transplant management should include consolidation treatment, but not many people would agree.

I believe their paper in the *British Journal of Haematology* is important. In fact, I am using post-transplant bortezomib-based consolidation for patients with poor-prognosis disease because that can potentially extend progression-free survival and overall survival.

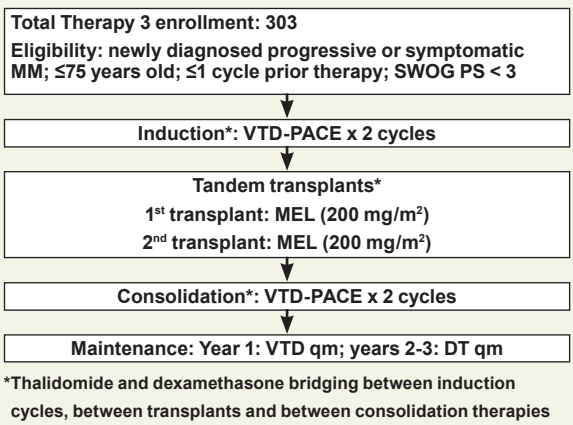
For patients with poor prognoses, there are no randomized trial data for bortezomib as maintenance therapy. So the recommendation for bortezomib is soft, and it comes from this Barlogie paper, which demonstrated that consolidation with a bortezomib-based regimen improves survival in patients with poor-prognosis cytogenetics. That's the only information we have.

Background

- **Total Therapy 2 (TT2) study evaluating up-front thalidomide in addition to intensive melphalan-based chemotherapy and ASCT demonstrated a five-year overall survival of 65%**
- **In the post-transplant salvage setting, VTD had a 60% PR rate and a 15% CR rate**
- **Total Therapy 3 (TT3) Phase II study evaluated the addition of VTD to PACE (cisplatin, doxorubicin, cyclophosphamide and etoposide) as induction and consolidation for high-dose melphalan in tandem transplants**

Source: Barlogie B et al. *Br J Haem* 2007;138(2):176-85. Abstract

Study Design



*Thalidomide and dexamethasone bridging between induction cycles, between transplants and between consolidation therapies

Source: Barlogie B et al. *Br J Haem* 2007;138(2):176-85. Abstract

Results

Two-year estimates*:	
Overall survival	86%
Event-free survival	84%
24-month cumulative frequency of nCR	83%
% of patients maintaining best response at two years from onset	
Complete response (CR)	90%
Near CR (nCR)	78%
Partial response	73%
Median postrelapse survival	12 months

***20-month median follow-up**

Source: Barlogie B et al. *Br J Haem* 2007;138(2):176-85. Abstract

>Grade II Toxicity by Protocol Stage

	Thromboembolic events*	Peripheral neuropathy
Postinduction (n = 303)	11%	14%
Post-transplant 1 (n = 285)	12%	10%
Post-transplant 2 (n = 251)	12%	11%
Postconsolidation (n = 218)	6%	11%
Postmaintenance (n = 164)	2%	13%

Treatment-related mortality: 5%

***27% cumulative nonfatal thromboembolic complications despite prophylactic low-molecular-weight heparin**

Source: Barlogie B et al. *Br J Haem* 2007;138(2):176-85. Abstract

Bortezomib, Doxorubicin and Dexamethasone (PAD) Front-Line Treatment of Multiple Myeloma: Updated Results After Long-Term Follow-Up

Popat R et al. *British Journal of Haematology* 2008;141(4):512-6.

FACULTY COMMENTS

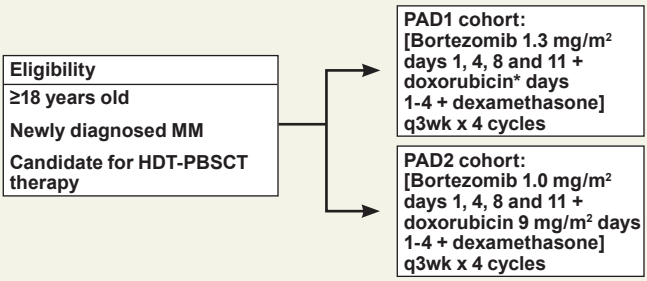
DR JAKUBOWIAK: Bortezomib combined with doxorubicin and dexamethasone (PAD) is an extremely active regimen, with overall and complete response rates that are almost identical to VdoxD in indirect comparison. It is a tolerable regimen and can be used pretransplant with rapid and effective cytoreduction and no impact on collection of stem cells. The flip side of PAD is a reasonably high rate of peripheral neuropathy, especially in the arm with the higher dose of bortezomib.

I consider PAD (or VdoxD), RVD and VDT to be the top three-drug regimens for initial cytoreduction of patients who have disease requiring rapid cytoreduction and who are potential candidates for transplant.

DR ORLOWSKI: I'm a big fan of anthracyclines, so I certainly like the combination. The concerns are the relatively high rate of neurotoxicity that was seen with the 1.3-mg/m^2 dose, although with the 1.0-mg/m^2 dose the neuropathy was much lower.

Design

Accrual: 41 (Closed)



***Escalating doxorubicin dose levels 1, 2 and 3: 0, 4.5 and 9 mg/m^2**

Source: Popat R et al. *Br J Haem* 2008;141(4):512-6. Abstract

Study Endpoints

Primary objective:

- **Evaluate feasibility of PBSC harvesting and post-HDT engraftment after PAD induction**

Secondary objectives:

- **Safety and toxicity assessment**
- **Overall response rate**
- **Progression-free survival**
- **Overall survival**
- **Time to re-treatment**

Source: Popat R et al. *Br J Haem* 2008;141(4):512-6. Abstract

PAD Induction: Efficacy

	PAD1 induction (n = 21)	PAD2 induction (n = 20)	*p*-value
Overall response rate Complete response (CR) Near CR Very good partial response Partial response	95% 24% 5% 33% 33%	89% 11% 5% 26% 47%	— — — — —
Median PFS*	29mo	24mo	0.1878
Median time to re-treatment	36mo	29mo	0.5156
One-year OS Two-year OS Median OS	100% 95% Not reached	95% 73% Not reached	— — 0.2193

***Median follow-up: PAD1, 40 months; PAD2, 24 months**

Source: Popat R et al. *Br J Haem* 2008;141(4):512-6. Abstract

Stem Cell Harvesting and Engraftment

	PAD1 (n = 21)	PAD2 (n = 20)
Peripheral blood stem cell harvesting success	95%	100%
Median yields x 10^6 CD34+ cells/kg (range)	3.75 (1.6-10.4)	5.15 (2.4-16)
Median time to neutrophil engraftment (range)	15 days (1-24)	15 days (6-28)
Median time to platelet engraftment (range)	13 days (10-33)	18 days (11-40)

Source: Popat R et al. *Br J Haem* 2008;141(4):512-6. Abstract

PAD Induction: Toxicities*

Select Grade III/IV toxicities	PAD2 induction (n = 20)
Liver function test results	15%
Psychiatric symptoms	10%
Thrombocytopenia	5%
Neutropenia	5%
Infection	5%
Pneumonia	5%
Sensory/painful neuropathy†	0% (9% Grade I/II)

***Toxicities for PAD1 cohort with doxorubicin dose escalation were previously reported; †In PAD1 cohort, 48% incidence, with 5% being Grade III**

Source: Popat R et al. *Br J Haem* 2008;141(4):512-6. Abstract

Melphalan, Prednisone and Lenalidomide Treatment for Newly Diagnosed Myeloma: A Report From the GIMEMA — Italian Multiple Myeloma Network

Palumbo A et al, on behalf of the GIMEMA — Italian Multiple Myeloma Network.
J Clin Oncol 2007;25(28):4459-65.

FACULTY COMMENTS

DR ORLOWSKI: With the melphalan/prednisone and thalidomide (MPT) regimen, one of the things that we would like to improve upon is the toxicity profile. Thalidomide is not an easy drug to administer to older patients who may have problems like constipation, sedation, thrombosis and infection. The feeling is that lenalidomide will be better tolerated overall.

This study had a Phase I component, which determined appropriate doses. Then a Phase II component examined the impact.

At the dose levels that were ultimately recommended for further therapy, MP with lenalidomide had a 100 percent response rate with minor responses or better. It is complicated by more hematologic toxicity than MPT, but those toxicities are probably a little easier to deal with.

This trial in part is the basis for one current Intergroup study in the US, which is comparing MPT versus MPR.

Patients and Methods

- **Phase I/II dose-escalating, noncomparative, open-label study (n = 54)**
- **Patient eligibility**
  - **Newly diagnosed multiple myeloma**
  - **>65 years old or <65 years old if ineligible for high-dose therapy**
  - **Platelets ≥ 75 x 10^9/L, neutrophils ≥ 1.5 x 10^9/L, serum Ca^{2+} < 3.5 mmol/L**
  - **No amyloidosis or other cancer**

Test doses	Melphalan (days 1-4)	Lenalidomide (days 1-21)	Prednisone (days 1-4)
1	0.18 mg/kg	5 mg	2 mg/kg
2	0.25 mg/kg	5 mg	2 mg/kg
3	0.18 mg/kg	10 mg	2 mg/kg
4	0.25 mg/kg	10 mg	2 mg/kg

Source: Palumbo A et al. *J Clin Oncol* 2007;25(28):4459-65. Abstract

Results: Efficacy of MPR at MTD

MTD = melphalan 0.18 mg/kg + prednisone 2 mg/kg + lenalidomide 10 mg

Endpoint (n = 21)	Percent
CR or VGPR	47.6%
PR	81%
One-year EFS	95.2%
One-year OS	100%

M = melphalan; P = prednisone; R = lenalidomide

Source: Palumbo A et al. *J Clin Oncol* 2007;25(28):4459-65. Abstract

Select Grade III/IV Adverse Events (AE) with MPR at MTD

MTD = melphalan 0.18 mg/kg + prednisone 2 mg/kg + lenalidomide 10 mg

Grade III/IV AE (n = 21)	Percent
Neutropenia	52.4%
Thrombocytopenia	23.8%
Febrile neutropenia	9.5%
Vasculitis	9.5%
Thromboembolism	4.8%

Source: Palumbo A et al. *J Clin Oncol* 2007;25(28):4459-65. Abstract

Prevention of Thalidomide- and Lenalidomide-Associated Thrombosis in Myeloma

Antonio Palumbo et al.
Leukemia 2008;22(2):414-23.

FACULTY COMMENTS

DR JAKUBOWIAK: This is an important paper based on a good analysis of the available data. Dr Palumbo and colleagues concluded that there are two good primary preventive measures for thrombosis, or VTE. Essentially, they stratified patients based on a number of risk factors. If there is less than or equal to one risk factor, they believe aspirin is appropriate. For patients with more than one risk factor, they recommend low molecular weight heparin or full-dose anticoagulation with warfarin.

A few years ago we were surprised to learn that lenalidomide-based regimens were associated with an increased risk of clotting. Previously, it was an obvious risk for thalidomide combinations, and it may also be true for some bortezomib-based combinations, so stratification of patients is important. This paper provides some guidelines and will decrease morbidity. I adopted this stratification strategy in my practice, and subsequently I have never had a patient experience a DVT.

Methods

- **Review of studies investigating prophylaxis for venous thromboembolism (VTE) in patients who received thalidomide or lenalidomide for the treatment of multiple myeloma**
- **Development of a prophylactic strategy according to a risk-assessment model**

Source: Palumbo A et al. *Leukemia* 2008;22(2):414-23. Abstract

Incidence of VTE in Trials of Thalidomide (T) or Lenalidomide (R) without Thromboprophylaxis

Treatment regimen	Newly diagnosed		Relapsed/refractory	
	VTE incidence		VTE incidence	
	T	R	T	R
Alone	3-4%	—	2-4%	0-33%
+ Dexamethasone	14-26%	8-75%	2-8%	8-16%
+ Melphalan	10-20%	—	11%	—
+ Doxorubicin	10-27%	—	58%*	—
+ Cyclophosphamide	3-11%	—	4-8%	14%
+ Multiagent chemo	16-34%	—	15%	—
+ Bortezomib	—	—	—	0%

***Both at diagnosis and relapse**

Source: Palumbo A et al. *Leukemia* 2008;22(2):414-23. Abstract

Incidence of VTE in Trials of Thalidomide (T) or Lenalidomide (R) with Thromboprophylaxis

	VTE incidence				
	LMWH	Low fixed-dose warfarin	Full-dose warfarin	Aspirin	
Treatment regimen	Thalidomide (T)			T	R
+ Dexamethasone	—	13-25%	8%	—	3-14%
+ Melphalan	3%	—	—	—	5%
+ Doxorubicin	9%	14%	—	18%	9%
+ Multiagent chemo	15-24%	31%	—	—	—

LMWH = low-molecular-weight heparin

Source: Palumbo A et al. *Leukemia* 2008;22(2):414-23. Abstract

Risk Assessment Model for MM: Patients Treated with T or R

- **Individual risk factors**
  - Obesity (BMI ≥ 30 kg/m^{-2})
  - Prior VTE
  - Central venous catheter or pacemaker
  - Associated disease
    - Cardiac disease
    - Chronic renal disease
    - Diabetes
    - Acute infection
    - Immobilization
  - Surgery
    - General surgery
    - Any anesthesia
    - Trauma
  - Medications
    - Erythropoietin
  - Blood clotting disorders
- **Myeloma-related risk factors**
  - Diagnosis
  - Hyperviscosity
- **Myeloma therapy risk factors**
  - High-dose dex (≥480 mg/month)
  - Doxorubicin
  - Multiagent chemo

Source: Palumbo A et al. *Leukemia* 2008;22(2):414-23. Abstract

Recommendations for the Management of VTE in Patients Treated for MM

- **Aspirin: Only for patients at low risk, such as those with no risk factors or one individual/myeloma-related risk factor**
- **LMWH or full-dose warfarin (INR 2-3):**
  - **At least two individual/myeloma-related risk factors**
  - **All patients receiving high-dose dexamethasone or doxorubicin or multiagent chemotherapy, independent of additional risk factors**

Source: Palumbo A et al. *Leukemia* 2008;22(2):414-23. Abstract

Neurotoxicity of Bortezomib Therapy in Multiple Myeloma: A Single-Center Experience and Review of the Literature

Badros A et al.
Cancer 2007;110(5):1042-9.

FACULTY COMMENTS

DR ORLOWSKI: Peripheral neuropathy is a complication of myeloma that can be particularly bothersome for patients and healthcare providers. Paul Richardson has data showing that up to 70 or 80 percent of newly diagnosed patients experience some element of neuropathy even before any drugs are introduced.

In addition, we know that some of the drugs we use can increase the incidence of neuropathy, or at least worsen the severity, including thalidomide, bortezomib and even other drugs like dexamethasone, which can be problematic if the patient develops diabetes.

In this retrospective analysis, they examined neurotoxicity, reviewing their own institutional experience and the literature. They emphasized the importance of following some of the dose-adjustment criteria that have been developed. Patients on bortezomib with worsening symptoms should be considered for early dose reduction because that's one of the best ways to reduce the potential for the neuropathy becoming permanent.

In deciding when to reduce the dose, we need to know the patient's baseline level of neuropathy so that we are aware when it begins to worsen. In patients with neuropathy at baseline, I try to intervene with agents that can help with symptoms, including gabapentin or tricyclic antidepressants.

Studies of bortezomib-associated neuropathy show that it tends to be slow in onset and the peak is usually not reached until the fifth cycle. I try to have a careful discussion with patients each cycle regarding their symptoms, and if there is any worsening, I start to consider reducing the dose from 1.3 to maybe 1.0 mg/m^2.

DR JAKUBOWIAK: This paper by Badros and colleagues essentially supports the prior observations reported by Dr Richardson that a high percentage of patients with newly diagnosed multiple myeloma experience neuropathy before treatment, and those patients with pre-existing peripheral neuropathy are at greater risk for exacerbation of those problems when treated with bortezomib.

Occurrence of Peripheral Neuropathy

	Number of patients*	
	Baseline	After bortezomib
Grade 0: Normal	48	22
Grade I: Loss of reflexes, or paresthesia without pain or loss of function	16	15
Grade II: Objective sensory loss; motor neuropathy interferes with function but not ADL	12	23
Grade III: Sensory loss or paresthesia; motor PN interferes with ADL	1	12
Grade IV: Disabling sensory or motor loss	0	6

***Number of patients treated = 78**

Source: Badros A et al. *Cancer* 2007;110(5):1042-9. Abstract

Risk Factors for Bortezomib Neurotoxicity

- **Factors not associated with incidence and grade of neuropathy**
  - **Age, sex, race**
  - **Creatinine level**
  - **Prior thalidomide**
  - **Whether bortezomib administered alone or combined with thalidomide, chemotherapy or dexamethasone**
- **Factors predictive of neuropathy**
  - **Prior neuropathy (p = 0.03)**
  - **Presence of diabetes (p = 0.03)**
- **Most peripheral neuropathy symptoms were reversible on stopping or reducing bortezomib**

Source: Badros A et al. *Cancer* 2007;110(5):1042-9. Abstract

Bortezomib in Relapsed Multiple Myeloma: Response Rates and Duration of Response are Independent of a Chromosome 13q-Deletion

Sagaster V et al.
Leukemia 2007;21:164-8.

FACULTY COMMENTS

DR ORLOWSKI: Data from the early Phase II studies suggested that patients with deletion 13 did well with bortezomib, which was later borne out in the APEX trial. This paper provided further follow-up and also examined other poor-risk features, such as a 4;14 translocation. The findings suggest that in patients with relapsed multiple myeloma, incorporation of bortezomib is important and improves outcomes in patients with these poor-risk features.

In Cavo's trial, comparing VTD versus TD, and Harousseau's VD versus VAD studies, patients with deletion in chromosome 13 did well with the bortezomib combinations. In the Italian study, VTD induced a better complete and near-complete response rate in cases of deletion 13 or a 4;14 translocation. However, we still don't know how durable the responses are. The problem with these patients has not necessarily been that their disease didn't respond, but that it didn't stay in a good response category, so we need long-term follow-up.

Results: Outcome by Del(13q14) Status

	13q-normal (n = 29)	Del(13q14) (n = 33)	*p*-value
Median time from initiation of first-line therapy to start of bortezomib	51mo	26mo	0.02
Overall response rate Complete response (CR)/near CR Partial response Minor response	55% 14% 38% 3%	45% 18% 21% 6%	0.66
Median duration of response	9.3mo	12.3mo	0.25
Median time to treatment failure	6.7mo	4.6mo	0.95
Median overall survival	Not yet reached	9.9mo	0.057

Source: Sagaster V et al. *Leukemia* 2007;21:164-8. Abstract

Impact of Translocations and Laboratory Parameters on Outcome

	Partial response	Median time to Rx failure	Median overall survival
Translocations t(14q32) translocation Present (n = 28) Absent (n = 31)	(*p* = 0.9) 50% 45%	(*p* = 0.29) 4.9mo 4.5mo	(*p* = 0.77) 16.7mo 14.6mo
t(4;14) (p16:q32) present (n = 3)	100%	11 to 40+ wk	NR
t(11;14)(q13:q32) present (n = 8)	25%	11 to 40+ wk	NR
Prognostic laboratory parameters $ß_2$-m high (>3.5 mg/L) low (≤3.5 mg/L) Serum albumin ≥3.5 g/dL <3.5 g/dL	 51% 49% 68% 32%	 5.0mo 4.4mo NR NR	 Not reached Not reached 22.6mo 7.7mo

NR = not reported

Source: Sagaster V et al. *Leukemia* 2007;21:164-8. Abstract

Abbreviations of Treatment Regimens Used in Clinical Case Scenarios

FCR	Fludarabine/cyclophosphamide/rituximab
MD	Melphalan/dexamethasone
MP	Melphalan/prednisone
MPT	Melphalan/prednisone/thalidomide
MPV	Melphalan/prednisone/bortezomib
PAD	Bortezomib (PS-341)/doxorubicin/dexamethasone
R-CHOP	Rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone
Rd	Lenalidomide/low-dose dexamethasone
RVD	Lenalidomide/bortezomib/dexamethasone
TD	Thalidomide/dexamethasone
VAD	Vincristine/doxorubicin/dexamethasone
VD	Bortezomib/dexamethasone
VdoxD	Bortezomib/pegylated liposomal doxorubicin/dexamethasone
VT	Bortezomib/thalidomide
VTD	Bortezomib/thalidomide/dexamethasone

Case 1a

55-yo with fatigue/anemia (HGB 9.5 gm/dl). Calculated globulin: 4.1 gm/dl. Calcium and creatinine: WNL. SPEP with immunofixation: IgG κ monoclonal gammopathy: 2.2 gm/dl. Quantitative immunoglobulins: Total IgG 3,000 mg/dl, with concomitant suppression of IgM and IgA. $ß_2$-microglobulin: 3.9 and serum albumin: 3.6 g/L. Bone marrow: 32% infiltration of plasma cells. Skeletal survey: Osteopenia, no obvious lytic lesions. FISH and cytogenetics: Normal.

What is generally your preferred initial treatment strategy?

1. Induction → single autologous stem cell transplant (ASCT), with collection of cells for a 2nd autograft
2. Induction → tandem ASCT
3. Induction → nonmyeloablative allogeneic transplant
4. Induction → transplant, depending on response
5. Other systemic therapy
6. Observation

Preferred treatment if the patient was 60? 65? 70? 75?

Faculty	55yo	60yo	65yo	70yo	75yo
Dr Jakubowiak	1	1	1	5	5
Dr Lonial	4	4	4	4	5
Dr Orlowski	1	1	1	1	5
Dr Richardson	1	1	4	5	5

Case 1b

55-yo with fatigue/anemia (HGB 9.5 gm/dl). Calculated globulin: 4.1 gm/dl. Calcium and creatinine: WNL. SPEP with immunofixation: IgG κ monoclonal gammopathy: 2.2 gm/dl. Quantitative immunoglobulins: Total IgG 3,000 mg/dl, with concomitant suppression of IgM and IgA. ß$_2$-microglobulin: 3.9 and serum albumin: 3.6 g/L. Bone marrow: 32% infiltration of plasma cells. Skeletal survey: Osteopenia, no obvious lytic lesions. FISH and cytogenetics: Normal.

What is generally your preferred initial treatment for this patient?

1. Rd
2. TD
3. VD
4. VTD
5. RVD
6. VAD
7. PAD
8. VdoxD
9. MP
10. MPT
11. MPV

Faculty	Response
Dr Jakubowiak	RVD
Dr Lonial	RVD
Dr Orlowski	VTD
Dr Richardson	RVD or VTD

Case 1c

55-yo with fatigue/anemia (HGB 9.5 gm/dl). Calculated globulin: 4.1 gm/dl. Calcium and creatinine: WNL. SPEP with immunofixation: IgG κ monoclonal gammopathy: 2.2 gm/dl. Quantitative immunoglobulins: Total IgG 3,000 mg/dl, with concomitant suppression of IgM and IgA. ß$_2$-microglobulin: 3.9 and serum albumin: 3.6 g/L. Bone marrow: 32% infiltration of plasma cells. Skeletal survey: Osteopenia, no obvious lytic lesions. FISH and cytogenetics: Normal.

Which dosing of dexamethasone would you generally use?

1. Low (40 mg weekly)
2. High (40 mg days 1-4, 9-12, 16-20)
3. Other

Faculty	Response
Dr Jakubowiak	Low
Dr Lonial	Other (20 mg on day of and day after bortezomib per RVD regimen)
Dr Orlowski	Other (per VTD regimen)
Dr Richardson	Low

Case 1d

If this 55-yo had adverse cytogenetics (eg, deletion 13 and/or translocation 4;14), what would generally be your preferred treatment?

1. Rd
2. TD
3. VD
4. VTD
5. RVD
6. VAD
7. PAD
8. VdoxD
9. MP
10. MPT
11. MPV

Faculty	Response
Dr Jakubowiak	VdoxD
Dr Lonial	RVD
Dr Orlowski	VTD
Dr Richardson	RVD

Case 1e

This 55-yo patient is treated with induction bortezomib/thalidomide with dexamethasone (VTD) and concurrent bisphosphonate and erythropoietin. A near complete response occurs, anemia resolves and paraprotein disappears, with immunofixation positivity alone. Bone marrow plasmacytosis returns to <5% and ß$_2$-microglobulin returns to WNL.

What would generally be your preferred approach to transplantation?

1. Single ASCT, with collection of cells for a 2nd transplant
2. Tandem ASCT
3. ASCT → allogeneic stem cell transplant
4. Miniallogeneic stem cell transplant
5. Full-intensity allogeneic stem cell transplant
6. Collection of stem cells for deferred transplant, continued thalidomide maintenance

Faculty	Response
Dr Jakubowiak	ASCT, collection of cells for 2nd transplant
Dr Lonial	Collection of stem cells for deferred transplant, continued thalidomide maintenance
Dr Orlowski	ASCT, collection of cells for 2nd transplant
Dr Richardson	ASCT, collection of cells for 2nd transplant

Case 1f

If an allogeneic stem cell transplant was desired and no related match could be identified, at this stage in the patient's course would you generally utilize a matched unrelated donor (MUD) allogeneic stem cell transplant?

1. Yes
2. No

Would you generally utilize MUD if the patient relapsed after 4-5 years?

1. Yes
2. No

Faculty	Generally utilize MUD	After 4-5 years
Dr Jakubowiak	No	No
Dr Lonial	No	No
Dr Orlowski	No	No
Dr Richardson	No	No

Case 1g

This 55-yo patient undergoes a single ASCT and remains asymptomatic. HGB is 13.6 gm/dl, creatinine is 1.1 mg/dl, and no M-protein is detected. Bone marrow plasmacytosis is 2%.

What is generally your approach to post-transplant management?

1. Surveillance only
2. Bisphosphonates alone
3. Steroids alone (± bisphosphonates)
4. Lenalidomide (± bisphosphonates)
5. Thalidomide (± bisphosphonates)
6. Lenalidomide or thalidomide with steroids (± bisphosphonates)
7. Bortezomib/thalidomide (± bisphosphonates)
8. Interferon

Faculty	Response
Dr Jakubowiak	Surveillance only
Dr Lonial	Bisphosphonates alone
Dr Orlowski	Surveillance only
Dr Richardson	Surveillance only or bisphosphonates alone

Case 1h

Assume that this 55-yo, with adverse cytogenetics (eg, deletion 13 and/or translocation 4;14), underwent a single ASCT and remained asymptomatic but had residual M-protein of 0.8. HGB 13.6 gm/dl and creatinine 1.1 mg/dl. Bone marrow plasmacytosis is 2%.

What would generally be your approach to post-transplant management?

1. Surveillance only
2. Bisphosphonates alone
3. Steroids (± bisphosphonates)
4. Lenalidomide (± bisphosphonates)
5. Thalidomide (± bisphosphonates)
6. Lenalidomide or thalidomide with steroids (± bisphosphonates)
7. Bortezomib/thalidomide (± bisphosphonates)
8. Interferon

Faculty	Response
Dr Jakubowiak	Bortezomib/thalidomide (± bisphosphonates)
Dr Lonial	Lenalidomide (± bisphosphonates)
Dr Orlowski	Bortezomib/thalidomide (± bisphosphonates)
Dr Richardson	Thalidomide (± bisphosphonates)

Case 1i

This 55-yo completed induction VTD and a transient Grade I neuropathy resolved post-transplant followed by HDT/ASCT. Treatment was then a bisphosphonate alone for 18 months, with no maintenance therapy. Patient working, with excellent quality of life. Now has a rising paraprotein (1.2 gm/dl). HGB is 11.2 gm/dl. Creatinine and calcium: WNL. Bone marrow: 15% plasma cells. Skeletal survey: Persistent osteopenia, 2 new lytic lesions.

What is generally your preferred initial treatment for this patient?

1. Rd
2. TD
3. VD
4. VTD
5. RVD
6. VAD
7. PAD
8. VdoxD
9. MP
10. MPT
11. MPV
12. Cyclophosphamide-based regimen

Faculty	Response
Dr Jakubowiak	RVD
Dr Lonial	RVD
Dr Orlowski	RVD
Dr Richardson	VD

Case 1j

This 55-yo was treated with a combination regimen for 12 weeks. After a modest response, the patient's status plateaus (paraprotein 0.4 gm/dl, HGB is 12.5 gm/dl). Bone marrow: 5% plasma cells.

What is generally your next therapeutic choice?

What would be your choice if the time to relapse after HDT/ASCT was 5 months? 54 months?

1. **A second ASCT**
2. **Miniallogeneic stem cell transplant if sibling match available**
3. **Full-intensity allogeneic stem cell transplant**
4. **I would not proceed to transplant, but salvage with bortezomib-based therapy**

Faculty	Next choice	5mo relapse	54mo relapse
Dr Jakubowiak	4	2	1
Dr Lonial	1	4	1
Dr Orlowski	2	2	1
Dr Richardson	4/2	4	1

Case 2a

A 60-yo presents with fatigue/anemia (HGB 9.5 gm/dl). Calculated globulin: 4.1 gm/dl. Calcium and creatinine: WNL. SPEP with immunofixation: IgG κ monoclonal gammopathy: 2.2 gm/dl. Quantitative immunoglobulins: Total IgG 3,000 mg/dl, with concomitant suppression of IgM and IgA. $ß_2$-microglobulin: 3.9 and serum albumin: 3.6 g/L. Bone marrow: 32% infiltration of plasma cells. Skeletal survey: Osteopenia, no obvious lytic lesions. FISH and cytogenetics: Normal.

What is generally your preferred treatment for this patient with newly diagnosed multiple myeloma, who elects to collect stem cells but defer transplantation?

1. **Rd**
2. **TD**
3. **VD**
4. **VTD**
5. **RVD**
6. **VAD**
7. **PAD**
8. **VdoxD**
9. **MP**
10. **MPT**
11. **MPV**

Faculty	Response
Dr Jakubowiak	Rd
Dr Lonial	RVD
Dr Orlowski	VTD
Dr Richardson	Rd or RVD or VTD

Case 2b

If this 60-yo had adverse cytogenetics (eg, deletion 13 and/or translocation 4;14), what would generally be your preferred treatment for this patient who elects to collect stem cells but defer transplantation?

1. Rd
2. TD
3. VD
4. VTD
5. RVD
6. VAD
7. PAD
8. VdoxD
9. MP
10. MPT
11. MPV

Faculty	Response
Dr Jakubowiak	RVD
Dr Lonial	RVD
Dr Orlowski	VTD
Dr Richardson	RVD or VTD

Case 3a

A 60-yo presented with sudden onset of severe back pain and compression fracture of L2, with multiple lytic lesions. HGB was 9.7 gm/dl, calcium was minimally elevated, creatinine was 2.0 mg/dl, IgG λ was 7.0 gm/dl, and ß$_2$-microglobulin was 7.8. 24-hour urine and electrophoresis: Positive for Bence Jones protein, and serum-free light chain was 2,000 mg/dl. Bone marrow: 62% infiltration of plasma cells, with multiple dysplastic large and multinucleated plasma cells. Adverse cytogenetics (eg, deletion 13, translocation 4;14). Patient is hospitalized and hydrated and bisphosphonates are administered.

What is generally your preferred treatment for this patient with newly diagnosed multiple myeloma?

1. Rd
2. TD
3. VD
4. VTD
5. RVD
6. VAD
7. PAD
8. VdoxD
9. MP
10. MPT
11. MPV

Faculty	Response
Dr Jakubowiak	VdoxD
Dr Lonial	RVD
Dr Orlowski	VTD
Dr Richardson	RVD or VTD

Case 3b

This 60-yo symptomatic patient had a partial response to induction VTD x 4 cycles, with IgG λ declining from 7.0 to 3.4 gm/dl. $ß_2$-microglobulin declined from 7.8 to 2.5, and bone marrow plasma cells decreased from 62% to 28%. His treatment course is complicated by treatment-emergent peripheral neuropathy.

Would you generally switch therapy to further cytoreduce?

1. **Yes**
2. **No**

What would generally be your preferred approach to transplantation?

1. **Single or tandem ASCT, dependent upon response to 1st transplant**
2. **ASCT → allogeneic stem cell transplant**
3. **Miniallogeneic stem cell transplant**
4. **Full-intensity allogeneic stem cell transplant**
5. **ASCT, cells collected for 2nd transplant**

Faculty	Switch to cytoreduce	Preferred approach
Dr Jakubowiak	Yes	1
Dr Lonial	No	1
Dr Orlowski	No	1
Dr Richardson	Yes	5

Case 3c

This 60-yo patient has less than 90% overall response to single ASCT, with a monoclonal spike of 0.7 gm/dl, $ß_2$-microglobulin 1.4, and bone marrow plasma cells measured at 7%.

What is generally your approach to ongoing care?

1. **Proceed with a 2nd ASCT**
2. **Miniallogeneic stem cell transplant**
3. **Maintenance therapy**

Faculty	Response
Dr Jakubowiak	Proceed with a 2nd ASCT
Dr Lonial	Proceed with a 2nd ASCT
Dr Orlowski	Proceed with a 2nd ASCT
Dr Richardson	Maintenance therapy

Case 4a

A 66-yo presented with sudden onset of severe back pain and compression fracture of L2, with multiple lytic lesions. HGB was 9.7 gm/dl, creatinine was 2.0 mg/dl, IgG λ was 4.8 gm/dl, and ß$_2$-microglobulin was 7.8. Bone marrow: 54% infiltration of plasma cells. Adverse cytogenetics were present (eg, deletion 13 and/or translocation 4;14).

What is generally your preferred treatment for this patient with newly diagnosed multiple myeloma?

1. MP
2. MPT
3. MPV
4. Rd
5. TD
6. VD
7. VTD
8. RVD
9. VAD
10. PAD
11. VdoxD

Faculty	Response
Dr Jakubowiak	VdoxD
Dr Lonial	RVD
Dr Orlowski	VTD
Dr Richardson	RVD or VTD

Case 4b

This 66-yo symptomatic patient has a partial response to induction MPV x 4 cycles and is tolerating treatment well, with IgG λ declining from 4.8 to 2.4 and infiltration of bone marrow with plasma cells decreased from 54% to 27%.

Would you switch therapy to further cytoreduce?

1. Yes
2. No

What would generally be your preferred approach to transplantation?

1. Single or tandem ASCT, dependent upon response to 1st transplant
2. ASCT → allogeneic stem cell transplant
3. Miniallogeneic stem cell transplant
4. Full-intensity allogeneic stem cell transplant
5. ASCT, with collection of cells for a 2nd transplant
6. No transplant, MPV x 59 wk

Faculty	Switch to cytoreduce	Preferred approach
Dr Jakubowiak	No	1
Dr Lonial	No	6
Dr Orlowski	No	1
Dr Richardson	No	5

Case 4c

This 66-yo patient has a less than complete response to single ASCT, with a monoclonal spike of 0.3 gm/dl, ß$_2$-microglobulin 1.4, and bone marrow plasma cells measured at 7%.

What is generally your approach to continued treatment?

1. **Proceed with a 2nd ASCT**
2. **Miniallogeneic stem cell transplant**
3. **Full-intensity allogeneic stem cell transplant**
4. **Maintenance therapy**

Faculty	Response
Dr Jakubowiak	Proceed with a 2nd ASCT
Dr Lonial	Maintenance therapy
Dr Orlowski	Miniallogeneic stem cell transplant
Dr Richardson	Maintenance therapy

Case 5

A 65-yo with newly diagnosed, mildly symptomatic, intermediate-risk multiple myeloma had a partial response to ASCT and therefore began maintenance thalidomide. Since diagnosis, patient was treated with monthly zoledronic acid for 1 year, and bone density has improved 8% but mild osteopenia remains.

What is generally your recommended approach for continued bisphosphonate treatment?

What would generally be your recommended approach if the patient had received 2 years of treatment with a bisphosphonate?

1. **Stop zoledronic acid**
2. **Continue monthly zoledronic acid**
3. **Decrease frequency of zoledronic acid to every 3 months**
4. **Decrease frequency of zoledronic acid to every 6 months**
5. **Decrease frequency of zoledronic acid to once yearly**

Faculty	After 1y of bisphosphonate	After 2y of bisphosphonate
Dr Jakubowiak	Continue monthly	Stop
Dr Lonial	↓ frequency to q3m	↓ frequency to q3m
Dr Orlowski	Continue monthly	Stop
Dr Richardson	↓ frequency to q3m	↓ frequency to q3m

Case 6

A 65-yo presented with high-risk multiple myeloma, with multiple lytic lesions and osteopenia. Patient had a partial response to ASCT and therefore began maintenance thalidomide. Since diagnosis, patient was treated with monthly zoledronic acid for 1 year, and bone density has improved 8% but mild osteopenia remains, with multiple lytic lesions that have not improved.

What is generally your recommended approach for continued bisphosphonate treatment?

What would generally be your recommended approach if the patient had received 2 years of treatment with a bisphosphonate?

1. **Stop zoledronic acid**
2. **Continue monthly zoledronic acid**
3. **Decrease frequency of zoledronic acid to every 3 months**
4. **Decrease frequency of zoledronic acid to every 6 months**
5. **Decrease frequency of zoledronic acid to once yearly**

Faculty	After 1y of bisphosphonate	After 2y of bisphosphonate
Dr Jakubowiak	Continue monthly	Stop
Dr Lonial	↓ frequency to q3m	↓ frequency to q3m
Dr Orlowski	Continue monthly	Stop
Dr Richardson	Continue monthly	Continue monthly

Case 7

In general, which bisphosphonate do you typically utilize in the treatment of multiple myeloma?

1. **Zoledronic acid**
2. **Pamidronate**
3. **Other**

In general, how frequently do you administer the bisphosphonate to a patient with osteopenia and no lytic lesions? For a patient with multiple lytic lesions?

1. **Monthly**
2. **Every 3 months**
3. **Every 6 months**
4. **Once per year**
5. **I would not administer a bisphosphonate**

Faculty	Bisphosphonate	No lytic lesions	With lytic lesions
Dr Jakubowiak	Pamidronate	Monthly	Monthly
Dr Lonial	Zoledronic acid	Monthly	Monthly
Dr Orlowski	Pamidronate	Monthly	Monthly
Dr Richardson	Pamidronate	Every 3 months	Monthly

Case 8

For a 70-yo with newly diagnosed multiple myeloma and renal insufficiency (creatinine 1.8 mg/dl), which bisphosphonate would you use?

1. Zoledronic acid
2. Pamidronate

If monthly zoledronic acid (ZA), how would you administer it?

1. Standard 4-mg IV in 30-min infusion
2. ↓ dose from 4 to 3 mg
3. ↑ infusion time from 30 to 60 min
4. ↓ dose and ↑ infusion time

If pamidronate, how would you administer it?

1. Standard 90-mg IV in 2-h infusion
2. ↓ dose from 90 to 60 mg
3. ↓ dose from 90 to 30 mg
4. ↑ infusion time from 2 to 4 h
5. ↓ dose and ↑ infusion time

Faculty	Bisphosphonate	Monthly ZA	Pamidronate
Dr Jakubowiak	Pamidronate	4	2
Dr Lonial	Pamidronate	4	5
Dr Orlowski	Pamidronate	4	2
Dr Richardson	Pamidronate	4	1

Case 9

For a 70-yo with newly diagnosed multiple myeloma and renal insufficiency (creatinine 2.5 mg/dl), which bisphosphonate would you generally use?

1. Zoledronic acid
2. Pamidronate

Faculty	Response
Dr Jakubowiak	Pamidronate
Dr Lonial	Pamidronate
Dr Orlowski	Pamidronate
Dr Richardson	Pamidronate

Case 10

A 60-yo presented with new-onset CHF, which was angiography-negative for coronary artery disease. Subcutaneous abdominal fat pad aspirate was positive for amyloidosis. SIEP revealed free light chain κ/λ of 20, with Bence Jones protein in the urine. Creatinine was 2.3, and the patient had albuminuria 5 gm/dl. Bone marrow: 8% infiltration with plasma cells.

What is generally your preferred treatment approach?

1. **MD**
2. **MP**
3. **MPV**
4. **Rd**
5. **TD**
6. **VTD**
7. **VAD**
8. **ASCT**

Faculty	Response
Dr Jakubowiak	MD
Dr Lonial	MD
Dr Orlowski	ASCT
Dr Richardson	MD or MPV

Case 11

A 70-yo smoker with high-risk multiple myeloma will be treated with bortezomib/thalidomide/dexamethasone (VTD). Three years ago, patient experienced a DVT without known precipitating factors. Treated with warfarin for 1 year.

What prophylactic anticoagulation therapy would you generally recommend?

1. **Warfarin 1 mg/day**
2. **Warfarin INR 2.0-3.0**
3. **Aspirin 81 mg/day**
4. **Aspirin 325 mg/day**
5. **Low-molecular-weight heparin (enoxaparin)**
6. **None**

Faculty	Response
Dr Jakubowiak	Low-molecular-weight heparin (enoxaparin)
Dr Lonial	Low-molecular-weight heparin (enoxaparin)
Dr Orlowski	Low-molecular-weight heparin (enoxaparin)
Dr Richardson	Low-molecular-weight heparin (enoxaparin)

Case 12

A 70-yo, who had pre-existing diabetes mellitus for 12 years and the onset of Grade I peripheral neuropathy in the lower extremities 4 years ago (with no current impact on his functioning), presents with high-risk multiple myeloma requiring treatment.

Which treatment would you generally recommend?

1. **MP**
2. **MPV**
3. **MPR**
4. **Rd**
5. **TD**
6. **VTD**
7. **VAD**

Faculty	Response
Dr Jakubowiak	MPV
Dr Lonial	VTD
Dr Orlowski	MPV
Dr Richardson	MPR or Rd

Case 13

A 70-yo, who had pre-existing diabetes mellitus for 12 years and the onset of peripheral neuropathy in the lower extremities 4 years ago (with an increased frequency of falls), presents with high-risk multiple myeloma.

Which treatment would you generally recommend?

1. **MP**
2. **MPV**
3. **MPR**
4. **Rd**
5. **TD**
6. **VTD**
7. **VAD**

Faculty	Response
Dr Jakubowiak	MPR
Dr Lonial	MPV
Dr Orlowski	Rd
Dr Richardson	MPR

Case 14

A 70-yo is responding to a bortezomib-containing regimen for intermediate-risk multiple myeloma but develops progressive peripheral neuropathy.

What is generally your approach to continued treatment?

1. **Switch to a nonbortezomib-containing regimen**
2. **Reduce the dose of bortezomib and continue treatment**

Faculty	Response
Dr Jakubowiak	↓ the dose of bortezomib and continue treatment
Dr Lonial	↓ the dose of bortezomib and continue treatment
Dr Orlowski	↓ the dose of bortezomib and continue treatment
Dr Richardson	↓ the dose of bortezomib and continue treatment

Case 15

A 70-yo undergoes treatment with thalidomide/dex (TD) for multiple myeloma. After 6 months, patient achieves a partial response and continues with thalidomide maintenance therapy, which is successful in controlling the disease. Patient develops progressive neuropathy despite dose reduction. After 9 months of treatment, the peripheral neuropathy is worsening, and thalidomide has been decreased to 50 mg/day without benefit.

What would you generally recommend next for this patient?

1. **Maintain thalidomide**
2. **Add back dexamethasone to thalidomide 50 mg/day**
3. **Reduce thalidomide to 50 mg every other day**
4. **Discontinue thalidomide, switch to another therapy**

Faculty	Response
Dr Jakubowiak	Discontinue thalidomide, switch to another therapy
Dr Lonial	Discontinue thalidomide, switch to another therapy
Dr Orlowski	Discontinue thalidomide, switch to another therapy
Dr Richardson	Discontinue thalidomide, switch to another therapy

Case 16

A 70-yo developed headaches and numbness of the fingers and toes. A CT C/A/P showed tiny vertebral lucencies, and IgM κ level was 7,300 mg/dl with serum viscosity of 2.60, bone marrow > 30% lymphoplasmacytoid cells, which were CD138-positive, CD5-negative, CD20 moderately positive, κ-positive and CD19-negative.

What would generally be your approach to initial therapy?

1. **Observation**
2. **Steroids and plasmapheresis**
3. **Bortezomib/thalidomide**
4. **Rituximab**
5. **FCR**
6. **R-CHOP**
7. **Bortezomib/rituximab/dexamethasone**

Faculty	Response
Dr Jakubowiak	Steroids and plasmapheresis
Dr Lonial	R-CHOP
Dr Orlowski	Steroids and plasmapheresis
Dr Richardson	Steroids and plasmapheresis or bortezomib/rituximab/dexamethasone

Case 17a

A 68-yo with a history of right eye trauma developed acute onset of right orbit swelling and pain. An MRI revealed a destructive lesion of bone. Blood work revealed an IgG λ monoclonal protein of 1.3 gm/dl, $ß_2$-microglobulin of 3.9 and calcium of 11.3 mg/dl. Urine electrophoresis was negative, and serum κ light chain was minimally elevated. Bone marrow studies were entirely normal. The patient is lucid, and bone survey revealed no additional abnormalities. PET/CT was negative.

What would generally be your approach to initial therapy?

1. **Observation**
2. **Radiation therapy with steroids**
3. **Radiation therapy with steroids and bisphosphonates**
4. **Bisphosphonates**
5. **TD**
6. **VTD**

Faculty	Response
Dr Jakubowiak	Radiation therapy with steroids
Dr Lonial	Radiation therapy with steroids
Dr Orlowski	Radiation therapy with steroids
Dr Richardson	Radiation therapy with steroids or radiation therapy with steroids and bisphosphonates

Case 17b

Suppose the patient were 55 years old. Would you generally recommend transplantation?

1. Yes
2. No

If yes, which would generally be your preferred approach to transplant?

1. Single ASCT
2. Tandem ASCT
3. ASCT → allogeneic stem cell transplant
4. Miniallogeneic stem cell transplant
5. Full-intensity allogeneic stem cell transplant

Faculty	Recommend transplantation?	Preferred approach
Dr Jakubowiak	No	NA
Dr Lonial	No	NA
Dr Orlowski	No	NA
Dr Richardson	No	NA

Case 18a

A 68-yo developed paraspinal soft tissue swelling centered 6 cm to the right of his T10 vertebral body. Imaging studies, including bone, revealed a solitary abnormality. Blood work revealed an IgG λ monoclonal protein of 1.3 gm/dl, $ß_2$-microglobulin of 3.9 and normal calcium level. A biopsy of the mass revealed sheets of plasma cells with IgG λ surface markers. Bone marrow studies were normal.

What would generally be your approach to initial therapy?

1. Observation
2. Radiation therapy with steroids
3. Bisphosphonates
4. TD
5. VTD

Faculty	Response
Dr Jakubowiak	Radiation therapy with steroids
Dr Lonial	Radiation therapy with steroids
Dr Orlowski	Radiation therapy with steroids
Dr Richardson	Radiation therapy with steroids

Case 18b

Suppose the patient were 55 years old. Would you consider transplantation?

1. Yes
2. No

If yes, which would generally be your preferred approach to transplant?

1. Single ASCT
2. Tandem ASCT
3. ASCT → allogeneic stem cell transplant
4. Miniallogeneic stem cell transplant
5. Full-intensity allogeneic stem cell transplant

Faculty	Recommend transplantation?	Preferred approach
Dr Jakubowiak	No	NA
Dr Lonial	No	NA
Dr Orlowski	No	NA
Dr Richardson	No	NA

Case 19

Low-dose dexamethasone rather than high-dose dexamethasone should be utilized when combined with:

A. Lenalidomide

1. Strongly agree
2. Agree
3. In between
4. Disagree
5. Strongly disagree

B. Thalidomide

1. Strongly agree
2. Agree
3. In between
4. Disagree
5. Strongly disagree

C. Bortezomib

1. Strongly agree
2. Agree
3. In between
4. Disagree
5. Strongly disagree

Faculty	Lenalidomide	Thalidomide	Bortezomib
Dr Jakubowiak	Strongly agree	Strongly agree	Strongly agree
Dr Lonial	Disagree	Strongly disagree	Agree
Dr Orlowski	Agree	Disagree	Disagree
Dr Richardson	Strongly agree	Agree	Agree

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the GIMEMA trial, comparing induction bortezomib/thalidomide/dexamethasone to thalidomide/dexamethasone in preparation for autologous stem cell transplantation, the addition of bortezomib _____ significantly increase the nCR/CR rate.**
   a. Did
   b. Did not
2. **In data from the Phase III trial of lenalidomide with high-dose versus low-dose dexamethasone for patients newly diagnosed with multiple myeloma, which regimen was associated with a superior overall survival rate?**
   a. Lenalidomide and high-dose dexamethasone
   b. Lenalidomide and low-dose dexamethasone
3. **In a Phase I/II study reported by Richardson et al evaluating bortezomib/lenalidomide/dexamethasone for patients with newly diagnosed multiple myeloma, the regimen _____ adversely affect stem cell harvesting in the majority of patients.**
   a. Did
   b. Did not
4. **In a retrospective analysis of Phase II and III trials, Jagannath et al concluded that bortezomib may overcome some of the adverse prognostic effects of chromosome 13 deletion.**
   a. True
   b. False
5. **In a multicenter, retrospective study by Chanan-Khan et al, which evaluated bortezomib for patients with multiple myeloma and advanced renal failure, the overall response rate and durability of responses were comparable to those among patients with primarily normal renal function treated with bortezomib.**
   a. True
   b. False
6. **In evaluating lenalidomide with dexamethasone for relapsed multiple myeloma, Weber et al reported that neutropenia was more common with the combination than with dexamethasone alone and could be managed with _____.**
   a. Dose adjustment
   b. G-CSF
   c. Both a and b
7. **Due to the increased risk of thromboembolic events with the combination of lenalidomide and dexamethasone used in the treatment of patients with relapsed or refractory multiple myeloma, routine use of prophylactic anticoagulants is recommended.**
   a. True
   b. False
8. **In Orlowski and colleagues' randomized Phase III study for patients with relapsed or refractory multiple myeloma, pegylated liposomal doxorubicin combined with bortezomib significantly improved which of the following compared to bortezomib alone?**
   a. Overall response rate
   b. Time to disease progression
   c. Both a and b
9. **In the VISTA trial, a Phase III study of bortezomib/melphalan/prednisone (VMP) or melphalan/prednisone (MP) for patients newly diagnosed with multiple myeloma, the complete response rate (immunofixation-negative) was _____ percent with VMP versus five percent with MP.**
   a. 10
   b. 22
   c. 35
   d. 60
10. **Harousseau et al reported that in a randomized trial evaluating induction treatments prior to autologous stem cell transplants in patients newly diagnosed with multiple myeloma, bortezomib/dexamethasone was well tolerated and significantly improved postinduction response rates when compared to vincristine/doxorubicin/dexamethasone.**
    a. True
    b. False
11. **In the clinical trial by Facon and colleagues evaluating melphalan/prednisone with or without thalidomide for elderly patients with previously untreated multiple myeloma, the addition of thalidomide significantly improved which of the following?**
    a. Median overall survival
    b. Median progression-free survival
    c. Response rate
    d. All of the above
12. **In the SWOG-S0232 trial presented by Zonder and colleagues, which evaluated high-dose dexamethasone with or without lenalidomide, the combination significantly improved which of the following?**
    a Complete response rate
    b. 12-month progression-free survival
    c. 12-month overall survival
    d. Both a and b
13. **In the Bologna 96 clinical study published by Cavo and colleagues, which evaluated single versus double autologous stem cell transplantation for multiple myeloma, a double transplant significantly prolonged overall survival.**
    a. True
    b. False
14. **In a trial by Ladetto et al evaluating bortezomib/thalidomide/dexamethasone as consolidation therapy following an autologous transplant, approximately _____ of the patients achieved complete remission after consolidation therapy.**
    a. 15 percent
    b. 32 percent
    c. 45 percent
    d. 66 percent
15. **In a clinical trial by Hulin et al evaluating melphalan/prednisone with or without thalidomide for patients age 75 and older newly diagnosed with Stage II or III multiple myeloma, the addition of thalidomide significantly improved which of the following?**
    a. Overall survival
    b. Progression-free survival
    c. Time to progression
    d. Response rate
    e. All of the above
16. **In a subset analysis of the APEX trial by Richardson et al, patients who were at high risk or elderly patients who received bortezomib for relapsed multiple myeloma experienced a _____ response rate compared to the overall study population.**
    a. Significantly lower
    b. Similar
    c. Significantly higher
17. **Data reported by San-Miguel et al showed that for patients with renal impairment who were treated with bortezomib, the efficacy of this agent was _____ to high-dose dexamethasone.**
    a. Inferior
    b. Superior
18. **Richardson et al reported that in the extended follow-up of the Phase III APEX trial, comparing bortezomib to high-dose dexamethasone for patients with relapsed multiple myeloma, the response rate with bortezomib _____ from the previously reported rate.**
    a. Increased
    b. Decreased
19. **According to Badros et al, factors predictive of neuropathy in patients with multiple myeloma receiving bortezomib include which of the following?**
    a. Creatinine level
    b. Presence of diabetes
    c. Prior neuropathy
    d. Prior thalidomide treatment
    e. Both b and c
    f. All of the above
20. **After long-term follow-up, updated results from Popat et al of the clinical trial evaluating bortezomib/doxorubicin/dexamethasone as front-line therapy for multiple myeloma indicated that this regimen is a highly effective induction regimen for untreated patients who are candidates for high-dose therapy with peripheral blood stem cell transplantation.**
    a. True
    b. False

Post-test answer key: 1a, 2b, 3b, 4a, 5a, 6c, 7a, 8b, 9c, 10a, 11d, 12d, 13b, 14d, 15e, 16b, 17b, 18a, 19e, 20a

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4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Incorporation of bortezomib- and IMiD-based regimens into the treatment of newly diagnosed MM 4 3 2 1
- Adverse cytogenetics and response to bortezomib- and IMiD-based regimens 4 3 2 1
- Unique side effects associated with bortezomib- and IMiD-based regimens 4 3 2 1
- Use of low-dose versus high-dose dexamethasone with lenalidomide 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Incorporation of bortezomib- and IMiD-based regimens into the treatment of newly diagnosed MM 4 3 2 1
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- Unique side effects associated with bortezomib- and IMiD-based regimens 4 3 2 1
- Use of low-dose versus high-dose dexamethasone with lenalidomide 4 3 2 1

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- Manage patients with MM considering recent advances related to front-line therapy, treatment of relapsed or refractory disease, maintenance and salvage therapy and autologous stem cell transplantation (ASCT). ..... 4 3 2 1 N/M N/A
- Develop a treatment plan for patients with MM who have compromised renal function. ..... 4 3 2 1 N/M N/A

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

.....

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.....

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.....

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Multiple Myeloma: 2007-2008

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