

# Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

April 2012

## Emerging Treatment Options for Relapsed and Refractory Multiple Myeloma: A Post-ASH Discussion

### Moderator



**David S. Siegel, MD, PhD**  
Chief of the Division of Multiple Myeloma  
Hackensack University Medical Center  
Hackensack, New Jersey

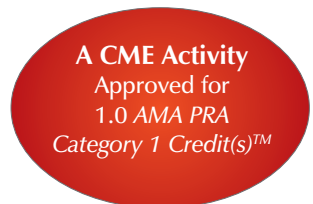
### Discussants



**Sundar Jagannath, MD**  
Director of the Multiple Myeloma Program  
Professor of Medicine (Hematology and Medical Oncology)  
The Tisch Cancer Institute  
Mount Sinai School of Medicine  
New York, New York



**Ruben Niesvizky, MD**  
Associate Attending Physician  
New York-Presbyterian Hospital  
Associate Professor of Medicine  
Weill Cornell Medical College  
New York, New York



**Release Date:** April 2012

**Expiration Date:** April 30, 2013

**Estimated time to complete activity:** 1 hour

**Project ID:** 8647

**Abstract:** Multiple myeloma is the second most common hematologic malignancy. Almost all patients who survive initial treatment will eventually relapse and require further therapy. Despite the availability of newer drugs such as bortezomib and lenalidomide, patients with relapsed or refractory multiple myeloma continue to have very limited treatment options and a restricted life expectancy. Several agents that have shown promise in treating relapsed or refractory multiple myeloma patients are currently in phase III clinical trials. Some of these novel agents work through new mechanisms, whereas others represent the next generation of existing medications. Agents with acceptable efficacy and low toxicity are better suited for relapsed patients who receive consecutive therapies. Moreover, agents with new mechanisms may be judiciously combined with existing agents to avoid overlapping toxicities.

Sponsored by the Postgraduate Institute for Medicine

Supported through an educational grant from Celgene Corporation and Onyx Pharmaceuticals, Inc.



Postgraduate Institute  
for Medicine

## Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and other health care professionals involved in the management of patients with multiple myeloma.

## Statement of Need/Program Overview

Multiple myeloma is the second most common hematologic malignancy. Almost all patients who survive initial treatment will eventually relapse and require further therapy. Despite the availability of newer drugs such as bortezomib and lenalidomide, patients with relapsed or refractory multiple myeloma continue to have very limited treatment options and a restricted life expectancy. However, several novel agents are under consideration by the US Food and Drug Administration. The 2011 American Society of Hematology meeting featured many clinical trials in relapsed or refractory multiple myeloma. Several novel agents attack the disease via new mechanisms. Other therapies represent the next generation of existing medications. These agents have been associated with significant improvements in patient outcomes.

## Educational Objectives

After completing this activity, the participant should be better able to:

- Utilize the best treatment options for patients with relapsed or refractory multiple myeloma based on recent clinical trial data
- Implement the most appropriate techniques for monitoring multiple myeloma
- Formulate evidence-based management plans for patients with multiple myeloma based upon their age, risk, and comorbidities
- Outline the most suitable goals for treatment of relapsed and refractory multiple myeloma as therapeutic options evolve

## Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Postgraduate Institute for Medicine and Millennium Medical Publishing. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians.

## Credit Designation

The Postgraduate Institute for Medicine designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

## Disclosure of Conflicts of Interest

Postgraduate Institute for Medicine (PIM) assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by PIM for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. PIM is committed to providing its learners with high-quality CME activities and related materials that promote improvements or quality in health care and not a specific proprietary business interest or a commercial interest.

The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

## Disclosures

**Ruben Niesvizky, MD**—Speakers bureau: Celgene Corporation, Millennium Pharmaceuticals, Inc., and Onyx Pharmaceuticals

**David S. Siegel, MD, PhD**—Honoraria: Celgene Corporation, Onyx Pharmaceuticals, and Millennium Pharmaceuticals, Inc.

**Sundar Jagannath, MD**—Consulting fees: Celgene, Millennium Pharmaceuticals, Merck, and BMS

The following PIM planners and managers, Laura Excell, ND, NP, MS, MA, LPC, NCC; Trace Hutchison, PharmD; Samantha Mattiucci, PharmD, CCMEP; Jan Schultz, RN, MSN, CCMEP; and Patricia Staples, MSN, NP-C, CCRN hereby state that they or their spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months. Maggie Merchant, PhD: No real or apparent conflicts of interest to report. Jacquelyn Matos: No real or apparent conflicts of interest to report.

## Method of Participation

There are no fees for participating in and receiving CME credit for this activity. During the period April 2012 through April 30, 2013, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test by recording the best answer to each question in the answer key on the evaluation form; 4) complete the evaluation form; and 5) mail or fax the evaluation form with answer key to Postgraduate Institute for Medicine. You may also complete the post-test online at [www.cmeuniversity.com](http://www.cmeuniversity.com). On the navigation menu, click on "Find Post-tests by Course" and search by project ID 8647. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed post-test with a score of 70% or better. Your statement of credit will be mailed to you within three weeks.

## Media

Monograph

## Disclosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. PIM, Millennium Medical Publishing, Celgene Corporation, and Onyx Pharmaceuticals, Inc. do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of PIM, Millennium Medical Publishing, Celgene Corporation, and Onyx Pharmaceuticals, Inc. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

## Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

## Disclaimer

Funding for this clinical roundtable monograph has been provided through an educational grant from Celgene Corporation and Onyx Pharmaceuticals, Inc. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc., the supporter, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

©2012 Millennium Medical Publishing, Inc., 611 Broadway, Suite 310, New York, NY 10012. Printed in the USA. All rights reserved, including the right of reproduction, in whole or in part, in any form.

# Introduction to Relapsed and Refractory Multiple Myeloma

Ruben Niesvizky, MD

**M**ultiple myeloma is a malignancy of clonal plasma cells. It is characterized by destructive bone lesions, hyperglycemia, renal failure, and the presence of paraproteinemia, as well as hematologic dysfunction. It is the second most common hematologic malignancy and is more frequent in individuals in the seventh or eighth decade of life.<sup>1,2</sup> With conventional therapy, the median survival has been approximately 3 years, but with the advent of novel agents, the survival has significantly improved.

Relapsed myeloma refers to a clinical scenario in which a patient who has been treated to a maximum response experiences progression of disease. Refractory myeloma refers to a clinical scenario in which the patient is not responsive to the current therapy or progresses within 2 months of the last treatment. Patients who fail to achieve any response whatsoever and then progress on therapy are especially challenging and fall into the category of primary refractory myeloma. Relapsed and refractory myeloma describes a patient who previously achieved a response, experienced progression of disease, received salvage therapy, and is either unresponsive to the salvage therapy proposed or progresses within 60 days of treatment.

The symptoms are usually confined to the organs that the disease affects. In most cases, this means bone, and bone pain occurs in 70–80% of patients.<sup>3</sup> The bones of the axial skeleton are most commonly affected. Patients suffer renal damage for many reasons, including the accumulation of light chains in the functional units of the kidney and its tubules. However, renal damage could be augmented or triggered by alterations in the fluid volume of patients with multiple myeloma, which may be caused by conditions such as hypercalcemia, dehydration, or infection. As the bone marrow is replaced by these neoplastic cells, the bone marrow function is altered. The presence of those malignancies in normal hematopoietic niches or the overproduction of inhibitory cytokines can induce paralysis of the normal functions of the bone marrow. That being said, other symptoms can appear in myeloma, such as hyperviscosity when the protein concentration (mostly immunoglobulin A) is high, or when other disorders are associated, such as amyloid light-chain amyloidosis.

It is important to define relapsed versus refractory disease, particularly in the context of clinical trials. To this end, the Multiple Myeloma Working Committee of the Autologous Bone Marrow Transplant Registry, an international bone marrow transplant registry, together with the European Group for Blood and Bone Marrow Transplantation, proposed criteria to standardize interpretation of disease progression and thus provide consistency across clinical trials and study centers.<sup>4,5</sup> Relapse from a complete response (CR) is defined by the reappearance of serum or urinary paraprotein, an incidence of more than 5% of clonal plasma cells, new bone lesions or new soft tissue plasmacytomas, an increase in the size of residual bone lesions, or the development of confirmed hypercalcemia that cannot be attributed to any other cause. All these parameters must be confirmed on 2 different occasions. Criteria for progressive disease when a CR has not been achieved include new or expanding bone lesions, hypercalcemia, or an increase of 25% in the monoclonal (M) protein concentration, 24-hour urine light chain excretion, or increased plasma cells in the bone marrow. The International Myeloma Working Group most recently revised the criteria specifying parameters for progression from CR by the presence of M protein increase based on immunofixation, and the group linked increased paraprotein in the blood or urine to specific concentrations.<sup>4</sup>

## Acknowledgment

*Dr. Niesvizky has received honoraria related to speakers bureau activities from Celgene Corporation, Millennium Pharmaceuticals, Inc., and Onyx Pharmaceuticals.*

## References

1. Surveillance, Epidemiology, and End Results (SEER). SEER Cancer Statistics Review 1975–2008. Myeloma. <http://seer.cancer.gov/statfacts/html/mulmy.html>. Accessed March 31, 2012.
2. American Cancer Society. Cancer Facts and Figures 2012. <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf>.
3. Kyle RA. Multiple myeloma: review of 869 cases. *Mayo Clin Proc.* 1975;50:29–40.
4. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia.* 2006;20:1467–1473.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. Version 1.2012. [http://www.nccn.org/professionals/physician\\_gls/recently\\_updated.asp](http://www.nccn.org/professionals/physician_gls/recently_updated.asp). Accessed March 31, 2012.

# Relapsed and Refractory Multiple Myeloma: Clinical Trials

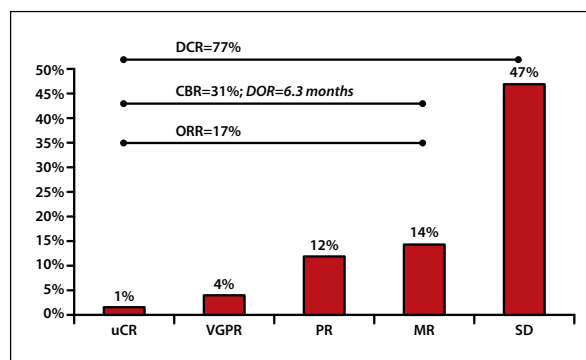
David S. Siegel, MD, PhD

Many clinical trials presented at the 2011 American Society of Hematology (ASH) meeting examined the treatment of relapsed and refractory multiple myeloma. Some of the data may be practice-changing.

## Phase III Trials of Vorinostat Plus Bortezomib

In 2 pivotal international trials, the combination of vorinostat, a histone deacetylase (HDAC) inhibitor, and bortezomib produced mixed results for patients with relapsed or refractory multiple myeloma. The phase IIb VANTAGE (Vorinostat Clinical Trials in Hematologic and Solid Malignancies) 095 trial enrolled 143 patients at very high risk whose disease was progressing at the time of study entry.<sup>1</sup> Patients were refractory to both lenalidomide and bortezomib. These patients have no other conventional therapeutic alternatives, and hence they represent an unmet medical need. The open-label, single-arm study enrolled patients with refractory disease or who were intolerant or ineligible for immunomodulatory drugs. Treatment consisted of bortezomib plus oral vorinostat. For patients whose disease did not respond after 4 cycles, oral dexamethasone could be added to treatment. The study population was heavily pretreated, with a median of 4 prior lines of therapy. The overall response rate (ORR) was 17%, which was clinically meaningful for this patient population. The clinical benefit rate, which included patients with a minimal response or better, was 31%. The disease control rate, encompassing patients whose best response was stable disease or better, was 77%. The overall survival (OS) for this study was 11.2 months. In the group of patients that showed a clinical benefit, the duration of response (DOR) was 6.3 months (Figure 1). Given the nature of the study population, the results represent a fairly robust response and show that the combination of vorinostat plus bortezomib is a viable treatment option for these patients.

In contrast, less impressive outcomes were observed in the VANTAGE 088 trial.<sup>2</sup> This international, multicenter, randomized, double-blind, phase III study included previously treated patients who were sensitive to bortezomib. The trial enrolled 637 patients with a median of 2 prior treatment regimens and randomized them 1:1 to receive bortezomib plus either vorinostat



**Figure 1.** Data from the phase IIb VANTAGE 095 trial, which evaluated a combination of vorinostat and bortezomib in patients at very high risk whose disease was progressing at the time of study entry. CBR=clinical benefit rate; DCR=disease control rate; DOR=duration of response; MR=minimal response; ORR=overall response rate; PR=partial response; SD=stable disease; uCR=complete response unconfirmed; VANTAGE=Vorinostat Clinical Trials in Hematologic and Solid Malignancies; VGPR=very good partial response. Adapted from Siegel DS et al. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 480.

or matching placebo. The combination treatment significantly improved ORR (56% vs 41%;  $P<.0001$ ) and the clinical benefit rate (71% vs 53%;  $P<.0001$ ) relative to the control arm. Duration of response (DOR) was similar in both arms (8.5 months for the combination vs 8.4 months for placebo). The combination treatment also increased progression-free survival (PFS) from 6.83 months to 7.63 months (hazard ratio [HR], 0.774; 95% CI, 0.64–0.94;  $P=.01$ ). Median OS was not significantly different between the 2 arms. Although there was a significant improvement in response rate and in the HR for progression, this did not translate into a significant improvement in event-free survival (EFS). Improvements were also noted for rates of partial response (PR; 28.3% vs 19.4%), very good partial response (VGPR; 20% vs 15.9%), and CR (7.9% vs 5.3%).

In summary, 2 very large trials had dichotomous outcomes. In the very heavily pretreated patient population that was entirely refractory to bortezomib, the addition of vorinostat to bortezomib seems to generate a significant response rate. Yet in a bortezomib-sensitive population, the

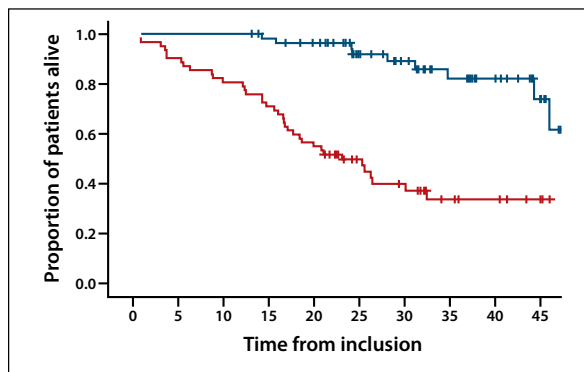
addition of vorinostat did not contribute to EFS, although it did slightly increase the depth of response and the number of responders. Although these findings can be interpreted in many ways, one view is that HDAC inhibitors work by resensitizing refractory patients to drugs that they have been exposed to previously. The findings were somewhat unusual. Rather than expanding the population that can be treated, the VANTAGE 088 study showed that the HDAC inhibitors are not as active in the relapsed-sensitive setting as they are in the relapsed-refractory setting.

## Smoldering Multiple Myeloma

Smoldering multiple myeloma is asymptomatic, but several factors predict high risk of progression to symptomatic disease. A study showed that the progression from pre-malignant to smoldering multiple myeloma to malignant multiple myeloma involves clonal expansion of deleterious plasma cells with specific genetic abnormalities, such as 13q deletions.<sup>3</sup> A related phase III trial (QuiReDex: Revlimid [Lenalidomide] and Dexamethasone [ReDex] Treatment Versus Observation in Patients With Smoldering Multiple Myeloma With High Risk of Progression) was designed to determine whether early treatment could prolong the time to progression (TTP) of patients with smoldering multiple myeloma.<sup>4</sup> High-risk patients were randomized to receive either no treatment or induction with lenalidomide plus dexamethasone followed by maintenance lenalidomide. The median TTP for the untreated arm was 23 months versus not yet reached for the treated arm. Of 118 evaluable patients, 59% of those randomized to no treatment converted to symptomatic myeloma compared with 15% of those who received the early treatment. Median 3-year OS was also significantly prolonged by the early treatment, reaching 93% with treatment versus 76% without ( $P=.04$ ; Figure 2). This study lends support to further investigations to validate these findings in high-risk patients with smoldering multiple myeloma.

## New Agents

One very intriguing presentation showed results from a novel chimeric antigen receptor (CAR), following on the work by Porter and colleagues in patients with chronic lymphoid leukemia.<sup>5</sup> When introduced into T cells, the CAR redirects the cells' specificity, reprogramming them to attack the malignant cells based on specific molecular determinants.<sup>6</sup> Mihara and colleagues transduced T cells from healthy donors with retroviral supernatant containing the anti-CD38 CAR and showed subsequent high expression of the chimeric molecule on the T cells. After showing specific killing against myeloma cell lines, the group showed that the engineered T cells achieved mean specific



**Figure 2.** In the QuiReDex trial, patients with smoldering multiple myeloma were randomized to receive either no treatment (red line) or induction with lenalidomide plus dexamethasone followed by maintenance lenalidomide (blue line). Benefit was seen with the treatment regimen. QuiReDex=Revlimid [Lenalidomide] and Dexamethasone [ReDex] Treatment Versus Observation in Patients With Smoldering Multiple Myeloma With High Risk of Progression. Adapted from Mateos VM et al. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 991.

toxicity of 90% against myeloma cells harvested from 5 different patients, and a 2:1 ratio of myeloma cells to T cells.

CD138 (syndecan-1) is highly overexpressed in various solid tumors as well as hematologic malignancies and is a specific marker of multiple myeloma cells. BT-062 is a monoclonal antibody drug conjugate that binds to CD138 and introduces the cytotoxic agent, DM4, into myeloma cells. Jagannath and associates performed an open-label, dose-escalation, multicenter, phase I study of BT-062 in relapsed/refractory multiple myeloma.<sup>7</sup> The study showed acceptable toxicity and evidence of activity, with stable disease or better observed in about half of the 27 evaluable patients.

Bendamustine is approved for treatment of chronic lymphocytic leukemia and indolent non-Hodgkin lymphoma. An open-label, phase I/II, dose-escalation study examined bendamustine in combination with lenalidomide and dexamethasone in patients with stage II or III multiple myeloma that was refractory to or had progressed after 1 or more prior therapies, including lenalidomide.<sup>8</sup> Based on results from 36 patients, the maximum tolerated dose (MTD) was 75 mg/m<sup>2</sup> for bendamustine and 10 mg for lenalidomide. The only reported severe toxicities were hematologic. After a median follow-up of 8 months, the estimated median PFS was 4.4 months (95% CI, 3.4–9.2), and median OS had not been reached.

## Proteasome Inhibitors

For the high-risk relapsed refractory population, the single most active drug now available appears to be carfilzomib,

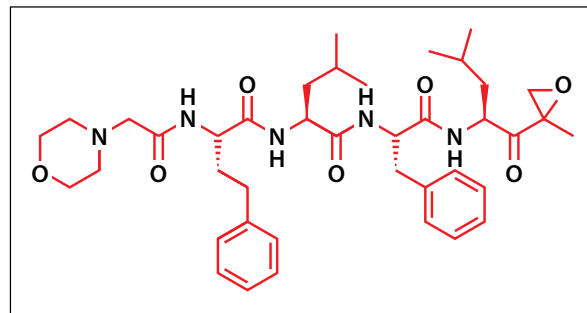


a novel proteasome inhibitor (Figure 3). PX-171-003-A1 was an open-label, single-arm, phase IIb trial that enrolled patients with multiply relapsed multiple myeloma who had received 2 prior therapies, including bortezomib, combined with either thalidomide or lenalidomide, and an alkylating agent.<sup>9</sup> The trial looked at carfilzomib in 2 dose schedules. The drug was given on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle at 20 mg/m<sup>2</sup> for the first cycle, then at 27 mg/m<sup>2</sup> for up to 12 subsequent cycles. The analysis of 257 evaluable patients revealed an ORR of 24% and a median DOR of more than 7 months. Notably, no treatment discontinuations occurred due to either new or increasing peripheral neuropathy. Median DOR of patients with minimal responses (MRs) was 6.3 months, reflecting that some patients had long-term MRs. The clinical benefit rate (comprising ORR plus MR) was 36%. Median DOR of patients with MRs was 6.3 months, indicating that some patients had long-term MRs. We found a very robust response, even in patients whose disease was refractory to prior treatments. It is important to mention that these patients were very heavily pretreated, having received a median 5 prior lines of therapy. The most common treatment-emergent, grade 3 adverse events were predominantly hematologic. Also of importance, carfilzomib produced virtually no high-grade peripheral neuropathy, which is of course the limiting toxicity of bortezomib.

Final phase I/II results were presented on the new combination of carfilzomib plus lenalidomide and dexamethasone in 53 newly diagnosed multiple myeloma patients.<sup>10</sup> This study in newly diagnosed patients is of interest here due to its inclusion of carfilzomib. The ORR was 94%, and all peripheral neuropathy observed was of grade 1 or 2. After 12 treatment cycles, 79% of patients achieved a complete or near-complete response, and responses were rapid.

Another novel proteasome inhibitor being tested in multiple myeloma is marizomib, which has shown efficacy in bortezomib-resistant cells in vitro and in vivo. Phase I data were presented on 34 patients who were treated with twice-weekly marizomib at doses ranging from 0.075–0.6 mg/m<sup>2</sup>, with or without low-dose dexamethasone.<sup>11</sup> The MTD was 0.5 mg/m<sup>2</sup> infused over 120 minutes, and drug-related adverse events were manageable. Marizomib did not appear to cause peripheral neuropathy or myelosuppression, which are common among patients treated with bortezomib. The drug showed modest efficacy, as 19% of evaluable patients achieved at least a PR and 38% achieved stable disease (SD), and activity was observed in patients with bortezomib-refractory disease.

MLN9708 is an orally available form of bortezomib that has shown very interesting results. A phase I/II study examined weekly treatment with this drug in combination



**Figure 3.** The structure of carfilzomib, a novel proteasome inhibitor.

with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma.<sup>12</sup> Although the MTD was found to be 2.97 mg/m<sup>2</sup>, a lower dose of 2.23 mg/m<sup>2</sup> has been recommended for the phase II trial based on better tolerability and no apparent loss of efficacy. The combination was generally well tolerated, with transient adverse events. Of the 15 patients enrolled, 100% achieved a PR, including 33% with VGPR and 27% with CR, after 4 treatment cycles. This drug has the potential to be very exciting for treating multiple myeloma.

### Other Novel Drugs of Interest

Elotuzumab is a humanized monoclonal antibody against CS1, which is highly expressed on the majority of multiple myeloma cells. Preclinical data showed activity in combination with lenalidomide in a mouse multiple myeloma xenograft model. Lonial and associates performed a phase II study of 73 patients who were randomized to receive elotuzumab at 10 mg/kg or 20 mg/kg in combination with lenalidomide and low-dose dexamethasone.<sup>13</sup> The most common treatment-emergent adverse events were lymphopenia, thrombocytopenia, and neutropenia, at 15–16% each. The ORR for both arms was 82%, with a higher response rate observed at the lower elotuzumab dose. After a median follow-up of 14.1 months, the median PFS had not been reached.

Panobinostat is an oral pan-DAC inhibitor that was examined in combination with bortezomib and dexamethasone in the phase II PANORAMA 2 (Panobinostat Oral in Multiple Myeloma) trial.<sup>14</sup> The patients in this single-arm study had relapsed, bortezomib-refractory disease and had received at least 2 prior lines of therapy. The treatment was given in 2 phases. During the first phase, patients received panobinostat, bortezomib, and dexamethasone during eight 3-week cycles. After 8 cycles, patients with a clinical benefit proceeded into the second phase, in which they were treated with the same drug combination every 6 weeks for 4 cycles. Results from 44 patients showed 9 patients with at least a PR, and 2 of

these patients had a near CR. Seven more patients had an MR. Of the 8 patients who advanced to the second treatment phase, 6 were still receiving treatment at the time of the presentation.

Phase II results from the phase I/II, MM-002 trial of pomalidomide alone or combined with low-dose dexamethasone were presented.<sup>15</sup> This study enrolled patients with relapsed/refractory disease that was resistant to lenalidomide and bortezomib, as pomalidomide activity had been observed in this setting. The recommended dose for the phase II portion was 4 mg/d, based on phase I findings reported at the 2010 American Society of Hematology (ASH) meeting.<sup>16</sup> In the open-label, phase II portion of the study, 221 heavily pretreated patients were randomized to receive pomalidomide with or without low-dose dexamethasone. There was an option to add low-dose dexamethasone to the monotherapy patients upon disease progression. In the combination arm, 34% achieved at least a partial response, compared with 13% of those given pomalidomide alone. PFS, the primary endpoint, was 3.8 months with dexamethasone and 2.5 months without (HR, 0.64; 95% CI, 0.47–0.66;  $P < .001$ ). The responses were rapid, with median DORs of 8.5 months with pomalidomide monotherapy versus 7.9 months with the combination. In lenalidomide-refractory patients, the portion of patients achieving at least a PR was improved with the combination therapy (29% vs 15%), and a similar trend was reported for double-refractory patients (30% vs 16%). Both regimens were well tolerated, and no grade 3/4 neuropathy was observed.

Lacy and associates reported on recently published outcomes from 2 phase II trials of daily pomalidomide (2 or 4 mg) in combination with weekly dexamethasone (40 mg) in patients who were refractory to both lenalidomide and bortezomib.<sup>17,18</sup> Each cohort enrolled 35 patients. The 2 mg and 4 mg cohorts yielded confirmed ORRs, including MR or better, of 49% and 43%, respectively. At 6 months, rates of OS were 78% and 67%, respectively.

Probably the single most important presentation from ASH that will immediately affect clinical practice was that by Moreau and associates showing the dramatic reduction in peripheral neuropathy with subcutaneous administration of bortezomib compared to intravenous administration. The study was designed to show noninferiority of the subcutaneous administration and indeed showed no significant difference in efficacy between the 2 routes of administration ( $P = .002$ ).<sup>19,20</sup> However, peripheral neuropathy was significantly reduced with subcutaneous administration, including any grade (38% vs 53%;  $P = .044$ ), grade 2 or higher (24% vs 41%;  $P = .012$ ), and grade 3 or higher (6% vs 16%;  $P = .026$ ). Peripheral neuropathy is the toxicity that most often results in bortezomib dose reductions or discontinuations. This group's

findings have already made a difference in how physicians manage patients with multiple myeloma and will continue to have an impact on patient management.

### Important Published Studies

The phase III BMT CTN 10102 study examined autologous stem cell transplantation followed by allogeneic or autologous stem cell transplantation in patients with standard-risk multiple myeloma.<sup>21</sup> Based on the endpoints of median EFS and median OS, the study failed to show improved efficacy with non-myeloablative allogeneic stem cell transplantation after autologous stem cell transplantation compared to tandem autologous transplantation. Specifically, in patients whose second transplant was allogeneic versus autologous, median 3-year PFS was 43% versus 46% ( $P = .671$ ), and median OS was 77% versus 80% ( $P = .191$ ). However, the study should be looking at long-term survival of 10 years post-transplant. In the past, we have seen studies in which the allotransplant arms have been markedly inferior to the autotransplant arms, but when the follow-up is long enough, there are many more long-term survivors in the allotransplant arm than in the autotransplant arm. Therefore, these data may be premature. Unfortunately, the results of this trial have led to insurance companies denying allogeneic treatment to multiple myeloma patients.

A publication of scientific interest was that describing cereblon expression as necessary for the activity of lenalidomide and thalidomide in myeloma.<sup>22</sup> The studies showed that cereblon presence was correlated to the activity of these drugs but was not correlated with the activity of unrelated drugs, such as bortezomib. It appears that cereblon may serve as a biomarker for the efficacy of immunomodulatory drugs.

The single most important study of this year described the complete sequencing of DNA from patients with multiple myeloma. The study performed parallel sequencing on 38 tumor genomes and compared them to matched normal DNA sequences.<sup>23</sup> Several unexpected somatic mutations were observed in genes involved in protein translation, histone methylation, coagulation, and in 11 members of the NF-kappa-B pathway. Activating mutations of BRAF kinase were observed in 4% of patients. The observed genomic heterogeneity underscores the fact that multiple myeloma is not a single disease.

A phase I/II study evaluated perifosine plus bortezomib with or without dexamethasone in 84 heavily pretreated patients with relapsed or relapsed multiple myeloma, all of whom had previous exposure to bortezomib.<sup>24</sup> Patients were treated with perifosine plus bortezomib alone, and dexamethasone was added upon disease progression. A response rate of 41% was observed

in 73 evaluable patients with at least a minimal response. Median PFS was 6.4 months, and median OS was 25 months. Although the results were modest, the triple therapy is being examined in a phase III trial versus bortezomib plus dexamethasone.

### Acknowledgment

Dr. Siegel has received honorarium from Celgene Corporation, Onyx Pharmaceuticals, and Millennium Pharmaceuticals, Inc.

### References

1. Siegel DS, Dimopoulos MA, Yoon SS, et al. Vantage 095: vorinostat in combination with bortezomib in salvage multiple myeloma patients: final study results of a global phase 2b trial. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 480.
2. Dimopoulos MA, Jagannath S, Yoon SS, et al. Vantage 088: vorinostat in combination with bortezomib in patients with relapsed/refractory multiple myeloma: results of a global, randomized phase 3 trial. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 811.
3. López-Corral L, Gutiérrez NC, Vidriales MB, et al. The progression from MGUS to smoldering myeloma and eventually to multiple myeloma involves a clonal expansion of genetically abnormal plasma cells. *Clin Cancer Res*. 2011;17:1692-1700.
4. Mateos VM, López-Corral L, Hernandez M, et al. Smoldering multiple myeloma (SMM) at high-risk of progression to symptomatic disease: a phase III, randomized, multicenter trial based on lenalidomide-dexamethasone (len-dex) as induction therapy followed by maintenance therapy with len alone vs no treatment. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 991.
5. Porter DL, Levine BL, Kalos M, Bagg A, and June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med*. 2011;365:725-733.
6. Mihara K, Bhattacharyya J, Kitanaka A, et al. T-cell immunotherapy with a chimeric receptor against CD38 is effective in eliminating myeloma cells. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 885.
7. Jagannath S, Chanan-Khan A, Heffner LT, et al. BT062, an antibody-drug conjugate directed against CD138, shows clinical activity in patients with relapsed or relapsed/refractory multiple myeloma. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 305.
8. Lentzsch S, O'Sullivan A, Kennedy R, et al. Combination of bendamustine, lenalidomide, and dexamethasone (BLD) in patients with refractory or relapsed multiple myeloma is safe and highly effective: results of phase I/II open-label, dose escalation study. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 304.
9. Siegel DS, Martin T, Wang M, et al. Results of PX-171-003-a1, an open-label, single-arm, phase 2 (Ph 2) study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM). Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 985.
10. Jakubowiak AJ, Dytfield D, Jagannath S, et al. Final results of a frontline phase 1/2 study of carfilzomib, lenalidomide, and low-dose dexamethasone (DRS) in multiple myeloma (MM). Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 631.
11. Richardson PG, Spencer A, Cannell P, et al. Phase 1 clinical evaluation of twice-weekly marizomib (NPI-0052), a novel proteasome inhibitor, in patients with relapsed/refractory multiple myeloma (MM). Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 302.
12. Berdeja JG, Richardson PG, Lonial S, et al. Phase 1/2 study of oral MLN9708, a novel, investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (MM). Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 479.
13. Lonial S, Jakubowiak AJ, Jagannath S, et al. A phase 2 study of elotuzumab in combination with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 303.
14. Richardson PG, Alsina M, Weber DM, et al. Phase II study of the pan-deacetylase inhibitor panobinostat in combination with bortezomib and dexamethasone in relapsed and bortezomib-refractory multiple myeloma (PANORAMA 2). Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 814.
15. Richardson PG, Siegel DS, Vij R, et al. Randomized, open label phase 1/2 study of pomalidomide (POM) alone or in combination with low-dose dexamethasone (LoDex) in patients (pts) with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide (LEN) and bortezomib (BORT): phase 2 results. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 634.
16. Richardson PG, Siegel D, Baz R, et al. A phase 1/2 multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose, safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib. Program and abstracts of the 52nd American Society of Hematology Annual Meeting and Exposition; December 4-7, 2010; Orlando, Florida. Abstract 864.
17. Lacy MQ, LaPlant BR, Laumann K, et al. Pomalidomide and dexamethasone in relapsed myeloma: results of 225 patients treated in five cohorts over three years. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 3963.
18. Lacy MQ, Allred JB, Gertz MA, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. *Blood*. 2011;118:2970-2975.
19. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomized, phase 3, non-inferiority study. *Lancet Oncol*. 2011;12:431-440.
20. Moreau P, Karamanesh II, Domnikova N, et al. Pharmacokinetics (PK) and pharmacodynamics (PD) of subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: effects of subcutaneous injection site and concentration, and patient characteristics. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 1863.
21. Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol*. 2011;12:1195-1203.
22. Zhu YX, Braggio E, Shi CX, et al. Cereblon expression is required for the anti-myeloma activity of lenalidomide and pomalidomide. *Blood*. 2011;118:4771-4779.
23. Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature*. 2011;471:467-472.
24. Richardson PG, Wolf J, Jakubowiak A, et al. Perifosine plus bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma previously treated with bortezomib: results of a multicenter phase I/II trial. *J Clin Oncol*. 2011;29:4243-4249.



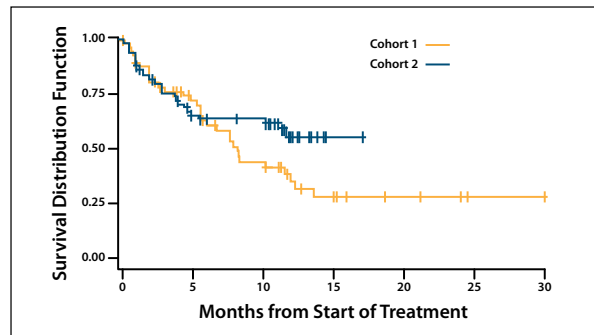
# Therapy Selection and Novel Agents in Relapsed and Refractory Multiple Myeloma

Sundar Jagannath, MD

**B**efore initiating re-treatment for a patient with multiple myeloma, it is necessary to ensure that the patient truly warrants therapy for recurrent disease. There are 2 defined parameters that determine which patients have truly relapsed and therefore should be treated: clinical relapse and significant paraprotein relapse. Clinical relapse refers to the presence of symptoms such as development of a new soft tissue plasmacytoma or bone lesion on imaging, a definite increase in existing plasmacytoma, increase in the bone lesion, hypercalcemia, anemia, renal dysfunction noted by rising serum creatinine, hyperviscosity, bone pain, or compression fracture. Paraprotein relapse is defined as patients whose M spike is doubling in 2 consecutive measurements separated by less than 2 months, or in 2 consecutive measurements, there is an absolute increase in serum M complement by more than 1 g/dL, a urine Bence-Jones protein measurement of more than 500 g/day, or increase in free light chain by 200 mg/L.<sup>1,2</sup>

## Therapy Selection

Choice of therapy for treatment of relapsed myeloma patients would be predicated on host-related factors, tumor-related factors, and prior treatment and response history. Patients presenting with renal impairment are better served by drugs that are independent of renal function, such as bortezomib, thalidomide, and cyclophosphamide. For patients presenting with significant cytopenia, non-myelosuppressive drugs, such as thalidomide, bortezomib, and glucocorticoids, are preferable. Patients who suffer from significant neuropathy should be spared additional exposure to thalidomide or bortezomib. Extramedullary presentation, elevated LDH, duplication of 1q+ in excess of 3 copies, and deletion 17p13 generally predict for poor prognosis and aggressive disease. It is better to use combination chemotherapy under these circumstances. In addition, there are treatment-related factors that depend upon the nature of the prior drug exposure. A patient who is progressing on bortezomib can be switched to lenalidomide, and vice versa. Another consideration is the nature of the relapse: whether it is indolent or aggressive and rapid, and whether it is the first relapse or one of many. These factors portend how the patient is going to fare on therapy, and therefore the treatment goal will differ for a patient



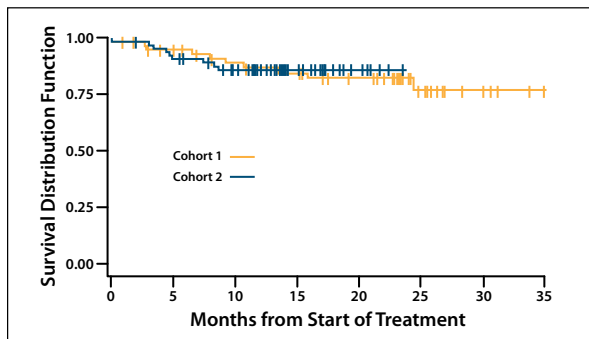
**Figure 4.** Progression-free survival of bortezomib-naïve patients with relapsed and/or refractory multiple myeloma in the PX-171-004, a phase 2 study of single-agent carfilzomib. Cohort 1: 20 mg/m<sup>2</sup>; Cohort 2: 20/27 mg/m<sup>2</sup>. Adapted from Vij R et al. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 813.

with indolent disease at first relapse versus a patient with aggressive, multiply relapsed disease.

Several options are available for salvage therapy, including bortezomib, lenalidomide, thalidomide, and chemotherapy, such as dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP). Transplant is another option if it was not part of the initial treatment.

## Novel Agents in Phase III Trials for the Relapsed Setting: Proteasome Inhibitors

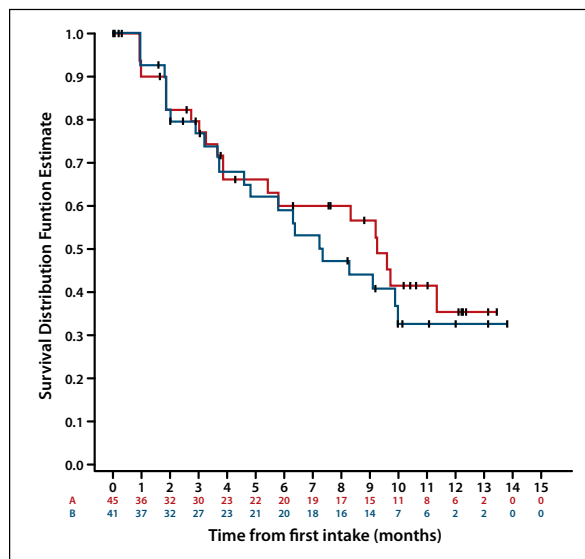
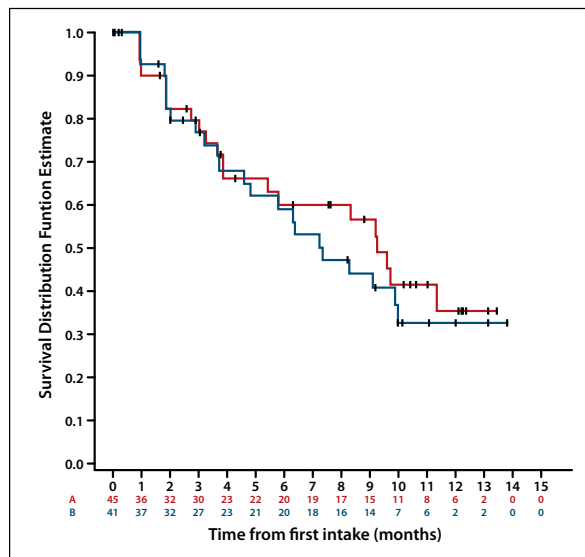
Carfilzomib is an irreversible proteasome inhibitor. It is an important new drug that targets the proteasome's chymotrypsin-like (CT-L) site, like bortezomib. Unlike bortezomib, carfilzomib is irreversible, and it can be given on consecutive days, so there is a prolonged exposure and it is highly selective with minimal off-target effects. This drug has been given in relapsed and refractory myeloma as a single agent in the PX-171-003 trial.<sup>3</sup> There were 2 different regimens: 20 mg/m<sup>2</sup> (cohort 1) and 20 mg/m<sup>2</sup> followed by 27 mg/m<sup>2</sup> (cohort 2). This study is interesting because most of the patients had received prior bortezomib. Among the 57 patients on the trial, ORR was 24%, median PFS was 3.7 months, and median overall survival was 15.5 months. In patients who had received 1 line of



**Figure 5.** Overall survival in bortezomib-naïve patients with relapsed and/or refractory multiple myeloma in the PX-171-004, a phase 2 study of single-agent carfilzomib. Cohort 1: 20 mg/m<sup>2</sup>; Cohort 2: 20/27 mg/m<sup>2</sup>. Adapted from Vij R et al. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 813.

prior bortezomib exposure, the overall response rate was 30%, but in patients who had received more than 1 line of prior bortezomib exposure, the RR decreased to 19%. Among patients who were bortezomib-refractory in the last line of therapy, the ORR decreased to 19%. Carfilzomib in bortezomib-naïve patients at 20 mg/m<sup>2</sup> showed an ORR of 42%.<sup>4</sup> With a dose of 20 mg/m<sup>2</sup> followed by 27 mg/m<sup>2</sup> in bortezomib-naïve patients, the RR increased to 52%. Both dosing regimens showed robust PFS and OS (Figures 4 and 5). Clearly, carfilzomib is a very active single agent. MLN9708 has a mechanism of action essentially identical to that of bortezomib, but MLN9708 is an oral compound. It also targets the chymotrypsin-like proteolytic site, but pharmacokinetic and pharmacodynamic studies suggest that the new generation drug may be more effective.<sup>5</sup> It was tested in a phase I trial of 46 evaluable patients, in which 21 patients were in the dose-escalation cohort and 30 patients were in the expansion cohort.<sup>6</sup> In this group of patients, 6 patients achieved partial remission or better, plus there was 1 patient with a CR, but this patient was never exposed to prior bortezomib.

Pomalidomide is a third-generation immunomodulatory drug. In the phase I portion of the MM-002 trial, the pomalidomide dose ranged from 2–5 mg, with the option to add dexamethasone.<sup>7,8</sup> Among the 28 patients who participated in the phase I study, 25% of the patients achieved at least a partial response, and the MTD was 4 mg. In the phase II portion of the trial, patients were randomized to pomalidomide 4 mg versus pomalidomide 4 mg plus low-dose dexamethasone. In the larger phase II trial, pomalidomide alone in 108 patients achieved an ORR of only 13% in this relapsed and refractory population. However, in the 113 patients treated with pomalidomide plus low-dose dexamethasone, the ORR was 34%, including 1 CR. The



**Figure 6.** In a study from the Intergroupe Francophone du Myélome, patients received pomalidomide 4 mg either continuously during a 28-day cycle (blue line) or in a cycle of 3 weeks on followed by 1 week off (red line). Better results were seen with the 3 weeks on and 1 week off schedule. Adapted from LeLeu X et al. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 812.

median PFS for pomalidomide plus low-dose dexamethasone was 4.7 months, whereas for pomalidomide alone it was 2.7 months. Median DOR was 7.9 months for the combination, and 8.5 months with pomalidomide alone.

Similar findings were reported by Lacy and colleagues.<sup>9,10</sup> Pomalidomide 2 mg with weekly dexamethasone 40 mg achieved an overall response rate of 34% in lenalidomide-refractory patients. In a study from the Intergroupe Francophone du Myélome, patients received pomalidomide 4 mg

either continuously during a 28-day cycle or in a cycle of 3 weeks on followed by 1 week off. Better results were seen with the 3 weeks on and 1 week off schedule (Figure 6).<sup>11</sup>

## DAC Inhibitors

As discussed by Dr. Siegel, the Vantage 095 trial examined bortezomib and vorinostat in relapsed and refractory myeloma patients.<sup>12</sup> The overall response rate was 17% and the clinical benefit response rate was 31%. The DOR, including minor response, was 6.3 months. The median overall survival was 11.2 months, with 2-year overall survival of 32%. The patients who received vorinostat plus bortezomib had a higher response rate that was highly significant, at 56% as compared to 41% for bortezomib plus placebo ( $P < .001$ ).<sup>13</sup> The clinical benefit response rate was 71% with vorinostat plus bortezomib versus 54% in placebo plus bortezomib. The OS data are too early to show any difference at this time. PFS was also improved in the combination arm, at 7.6 months compared to 6.8 months. Although the improvement was less than 1 month, it was statistically significant and therefore met the study objective. Vorinostat is now being considered for approval by the FDA.

In the phase II PANORAMA 2 study, panobinostat, a pan-DAC inhibitor, bortezomib, and dexamethasone were evaluated for safety and efficacy in 55 bortezomib-refractory myeloma patients.<sup>14</sup> The ORR was 29%. Phase III trial results are forthcoming.

## Monoclonal Antibodies

Lonial and colleagues presented a phase II study of elotuzumab in combination with lenalidomide and low-dose dexamethasone.<sup>15</sup> Patients were randomized to receive elotuzumab at either 10 mg/m<sup>2</sup> or 20 mg/m<sup>2</sup>. Elotuzumab, at 10 mg/kg, combined with lenalidomide, achieved an ORR of 92%, compared to approximately 60% with lenalidomide and dexamethasone. In addition, the responses were durable: at a median follow-up of 14.1 months, the median PFS was not reached in the elotuzumab/lenalidomide group. In the lenalidomide/dexamethasone group, the median PFS was 11.1 months. This drug is very promising, and there is a phase III clinical trial now ongoing.

Two antibodies are currently being tested in phase 3 trials in combination with other active myeloma agents, namely elotuzumab and siltuximab.<sup>15</sup> Elotuzumab binds to antigen CS 1 expressed on plasma cells universally. Elotuzumab in combination with lenalidomide and dexamethasone showed a very high response rate of 82% in patients with multiple myeloma with

1 to 3 prior relapses. Siltuximab binds to IL-6 and was combined with dexamethasone in a phase II study. A response was seen in 17% of patients, and a further 6% had an MR.<sup>16</sup>

## Perifosine

Preclinical data with perifosine, an AKT inhibitor, showed good synergy with several myeloma drugs. An early phase I/II trial reported by Richardson and colleagues with perifosine and bortezomib with or without dexamethasone showed an ORR (including MRs) of about 41% for this combination in 73 evaluable patients, whereas in bortezomib-refractory patients, 32% of the patients responded.<sup>17</sup> This drug is also being tested in a phase III study.

## Acknowledgment

*Dr. Jagannath has received consulting fees from Celgene, Millennium Pharmaceuticals, Merck, and BMS.*

## References

1. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20:1467-1473.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. Version 1.2012. Accessed [http://www.nccn.org/professionals/physician\\_gls/recently\\_updated.asp](http://www.nccn.org/professionals/physician_gls/recently_updated.asp). Accessed March 31, 2012.
3. Siegel DS, Martin T, Wang M, et al. Results of PX-171-003-a1, an open-label, single-arm, phase 2 (Ph 2) study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM). Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 4-7, 2010; Orlando, Florida. Abstract 985.
4. Vij R, Kaufman JL, Jakubowiak AJ, et al. Final results from the bortezomib-naïve group of PX-171-004, a phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory MM. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 813.
5. Kupperman E, Lee EC, Cao Y, et al. Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer. *Cancer Res*. 2010;70:1970-1980.
6. Berdeja JG, Richardson PG, Lonial S, et al. Phase 1/2 study of oral MLN9708, a novel, investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (MM). Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 479.
7. Richardson PG, Siegel D, Baz R, et al. A phase 1/2 multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose, safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib. Program and abstracts of the 52nd American Society of Hematology Annual Meeting and Exposition; December 4-7, 2010; Orlando, Florida. Abstract 864.
8. Richardson PG, Siegel DS, Vij R, et al. Randomized, open label phase 1/2 study of pomalidomide (POM) alone or in combination with low-dose dexamethasone (LoDex) in patients (pts) with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide (LEN) and bortezomib (BORT): phase 2 results. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 634.
9. Lacy MQ, LaPlant BR, Laumann K, et al. Pomalidomide and dexamethasone in relapsed myeloma: results of 225 patients treated in five cohorts over three years. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 3963.

10. Lacy MQ, Allred JB, Gertz MA, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. *Blood*. 2011;118:2970-2975.
11. LeLeu X, Attal M, Arnulf B, et al. High response rates to pomalidomide and dexamethasone in patients with refractory myeloma, final analysis of IFM 2009-02. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 812.
12. Siegel DS, Dimopoulos MA, Yoon SS, et al. Vantage 095: vorinostat in combination with bortezomib in salvage multiple myeloma patients: final study results of a global phase 2b trial. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 480.
13. Dimopoulos MA, Jagannath S, Yoon SS, et al. Vantage 088: vorinostat in combination with bortezomib in patients with relapsed/refractory multiple myeloma: results of a global, randomized phase 3 trial. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 811.
14. Richardson PG, Alsina M, Weber DM, et al. Phase II study of the pan-deacetylase inhibitor panobinostat in combination with bortezomib and dexamethasone in relapsed and bortezomib-refractory multiple myeloma (PANORAMA 2). Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 814.
15. Lonial S, Jakubowiak AJ, Jagannath S, et al. A phase 2 study of clotuzumab in combination with lenalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 303.
16. Voorhees PM, Manges RF, Sonneveld P, et al. A phase 2 multicenter study of siltuximab, an anti-il-6 monoclonal antibody, in patients with relapsed or refractory multiple myeloma. Program and abstracts of the 53rd American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 3971.
17. Richardson PG, Wolf J, Jakubowiak A, et al. Perifosine plus bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma previously treated with bortezomib: results of a multicenter phase I/II trial. *J Clin Oncol*. 2011;29:4243-4249.

# Slide Library

## Multiple Myeloma: Relapsed and Refractory

- Relapsed myeloma refers to a clinical scenario in which a patient who has been treated to a maximum response experiences progression of disease
- Refractory myeloma refers to a clinical scenario in which the patient is not responsive to the current therapy or progresses within 2 months of the last treatment
- Patients who fail to achieve any response fall into the category of primary refractory myeloma
- Relapsed and refractory myeloma describes a patient who previously achieved a response, experienced progression of disease, received salvage therapy, and is either unresponsive to salvage therapy or progresses within 60 days of treatment

## Multiple Myeloma: Symptoms

- Bone pain, most often in the axial skeleton
- Renal damage
- Paralysis of the normal functions of the bone marrow
- Hyperviscosity

## Interpretation of Disease Progression: Relapse

Relapse from a complete response is defined by:

- The reappearance of serum or urinary paraprotein
- An incidence of more than 5% of clonal plasma cells
- New bone lesions or new soft tissue plasmacytomas
- An increase in the size of residual bone lesions
- The development of confirmed hypercalcemia that cannot be attributed to any other cause

## Interpretation of Disease Progression: Progressive Disease

Criteria for progressive disease when a complete response has not been achieved include:

- New or expanding bone lesions
- Hypercalcemia
- An increase of 25% in the monoclonal protein concentration, 24-hour urine light chain excretion, or increased plasma cells in the bone marrow

## The Phase IIb VANTAGE 095 Trial

Patient Population (N)	Treatment	Outcome
Patients with very high-risk, progressive disease who were refractory to both lenalidomide and bortezomib (N=143)	Bortezomib plus oral vorinostat. For patients whose disease did not respond after 4 cycles, oral dexamethasone could be added	ORR, 17% Clinical benefit rate, 31% Overall survival, 11.2 months Duration of response, 6.3 months

VANTAGE=Vorinostat Clinical Trials in Hematologic and Solid Malignancies.  
Data from: Siegel DS et al. Program and abstracts of the 53 American Society of Hematology Annual Meeting and Exposition, December 10-13, 2011, San Diego, California, Abstract 486.

## Bortezomib: Routes of Administration

- Peripheral neuropathy is the toxicity that most often results in bortezomib dose reductions or discontinuation
- A study by Moreau and associates showed no significant difference in efficacy between subcutaneous and intravenous administration
- Subcutaneous administration was associated with significantly reduced peripheral neuropathy, including any grade (38% vs 53%;  $P=.044$ ), grade 2 or higher (24% vs 41%;  $P=.012$ ), and grade 3 or higher (6% vs 16%;  $P=.026$ )

Data from: Moreau P et al. *Lancet Oncol.* 2011;12:431-440.



## New Drugs in the Pipeline

### Agents in Phase III Studies

Target	Combination Partner/s
1. Pomalidomide	Dexamethasone
2. Carfilzomib	Lenalidomide and Dexamethasone
3. Vorinostat	Bortezomib
4. Panobinostat	Bortezomib
5. Elotuzumab	Lenalidomide and Dexamethasone
6. Perifosine	Bortezomib
7. Siltuximab	Bortezomib

## Cell Surface Targets

Target	Agent
CS-1	Elotuzumab
IL-6	Siltuximab
CD40	anti-CD40 Ab
CD56	huN901-DM1
CD138	BT-062
IGF1R	Anti-IGF1R Ab
FGFR3	CHIR258 inhibitor, PKC412
DKK-1	anti-DKK-1 Ab
BAFF	LY2127399 anti-BAFF Ab
CD70	anti-CD70 Ab
CD27	anti-CD27 Ab

## The Phase IIb PX-171-003-A1 Trial

Patient Population (N)	Treatment	Outcome
Patients with multiply relapsed multiple myeloma who had received 2 prior therapies, including bortezomib, combined with either thalidomide or lenalidomide, and an alkylating agent (N=257)	Carfilzomib in 2 dose schedules: given on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle at 20 mg/m <sup>2</sup> for the first cycle, then at 27 mg/m <sup>2</sup> for up to 12 subsequent cycles	ORR, 24% Median duration of response, more than 7 months

Data from: Siegel DS et al. Program and abstracts of the 53 American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 985.

## Phase II Results From the MM-002 trial

Patient Population (N)	Treatment	Outcome
Patients with relapsed/refractory disease that was resistant to lenalidomide and bortezomib (N=221)	Pomalidomide (4 mg/d) with or without low-dose dexamethasone	In the combination arm, 34% achieved at least a partial response, compared with 13% of those given pomalidomide alone. PFS was 3.8 months with dexamethasone and 2.5 months without

Data from: Richardson PG et al. Program and abstracts of the 53 American Society of Hematology Annual Meeting and Exposition; December 10-13, 2011; San Diego, California. Abstract 634.

For a free electronic download of these slides, please direct your browser to the following web address:

[http://www.clinicaladvances.com/index.php/our\\_publications/hem\\_onc-issue/ho\\_april\\_2012/](http://www.clinicaladvances.com/index.php/our_publications/hem_onc-issue/ho_april_2012/)

## Emerging Treatment Options for Relapsed and Refractory Multiple Myeloma: A Post-ASH Discussion

**CME Post-Test:** Circle the correct answer for each question below.

1. Refractory myeloma refers to a clinical scenario in which the patient is not responsive to the current therapy or progresses \_\_\_\_\_.
  - a. within 2 months of the last treatment
  - b. within 3 months of the last treatment
  - c. within 4 months of the last treatment
  - d. within 5 months of the last treatment
2. In the phase IIb VANTAGE 095 trial, which examined bortezomib plus oral vorinostat in patients at very high risk, the overall response rate was \_\_\_\_\_.
  - a. 13%
  - b. 15%
  - c. 17%
  - d. 19%
3. In an open-label, phase I/II, dose-escalation study examining bendamustine, lenalidomide, and dexamethasone in patients with stage II or III multiple myeloma that was refractory or had progressed, what was the maximum tolerated dose of lenalidomide?
  - a. 8 mg
  - b. 10 mg
  - c. 12 mg
  - d. 14 mg
4. For the high-risk relapsed refractory population, the single most active drug now available appears to be \_\_\_\_\_.
  - a. Bortezomib
  - b. Carfilzomib
  - c. Dexamethasone
  - d. Elotuzumab
5. In the phase II PANORAMA 2 trial examining a regimen of panobinostat, bortezomib, and dexamethasone, how many patients achieved at least a partial response?
  - a. 9
  - b. 10
  - c. 11
  - d. 12
6. In a study by Moreau of bortezomib, which route of administration showed a reduction in peripheral neuropathy?
  - a. Enteral
  - b. Intravenous
  - c. Oral
  - d. Subcutaneous
7. In a phase II study, elotuzumab at 10 mg/kg combined with lenalidomide achieved an overall response rate of \_\_\_\_\_.
  - a. 71%
  - b. 75%
  - c. 83%
  - d. 92%
8. Which agent binds to the epidermal growth factor receptor?
  - a. Cetuximab
  - b. Panobinostat
  - c. Perifosine
  - d. Siltuximab
9. In a study by Lacy and colleagues of pomalidomide, which schedule was associated with better results?
  - a. Continuous administration during a 28-day cycle
  - b. Administration for 3 weeks on followed by 1 week off
10. In an early phase I/II trial reported by Richardson and colleagues, perifosine and bortezomib with or without dexamethasone showed an overall response rate of approximately \_\_\_\_\_.
  - a. 41%
  - b. 51%
  - c. 61%
  - d. 71%

# Evaluation Form: Emerging Treatment Options for Relapsed and Refractory Multiple Myeloma: A Post-ASH Discussion

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. *You must complete this evaluation form to receive acknowledgment for completing this activity.*

**Please rate your level of agreement by circling the appropriate rating:**

1 = Strongly Disagree    2 = Disagree    3 = Neutral    4 = Agree    5 = Strongly Agree

**Learning Objectives**

After participating in this activity, I am now better able to:

- |   |   |   |   |   |   |
|---|---|---|---|---|---|
| 1. Utilize the best treatment options for patients with relapsed or refractory multiple myeloma based on recent clinical trial data | 1 | 2 | 3 | 4 | 5 |
| 2. Implement the most appropriate techniques for monitoring multiple myeloma  | 1 | 2 | 3 | 4 | 5 |
| 3. Formulate evidence-based management plans for patients with multiple myeloma based upon their age, risk, and comorbidities       | 1 | 2 | 3 | 4 | 5 |
| 4. Outline the most suitable goals for treatment of relapsed and refractory multiple myeloma as therapeutic options evolve          | 1 | 2 | 3 | 4 | 5 |

**Based upon your participation in this activity, choose the statement(s) that apply:**

- I gained new strategies/skills/information that I can apply to my area of practice.
- I plan to implement new strategies/skills/information into my practice.
- I need more information before I can implement new strategies/skills/information into my practice behavior.
- This activity will not change my practice, as my current practice is consistent with the information presented.
- This activity will not change my practice, as I do not agree with the information presented.

**What strategies/changes do you plan to implement into your practice?** \_\_\_\_\_

**How confident are you that you will be able to make this change?**

- Very confident                       Unsure
- Somewhat confident               Not very confident

**What barriers do you see to making a change in your practice?** \_\_\_\_\_

**Please rate your level of agreement by circling the appropriate rating:**

1 = Strongly Disagree    2 = Disagree    3 = Neutral    4 = Agree    5 = Strongly Agree

**The content presented:**

- |  |   |   |   |   |   |
|--|---|---|---|---|---|
| Enhanced my current knowledge base   | 1 | 2 | 3 | 4 | 5 |
| Addressed my most pressing questions   | 1 | 2 | 3 | 4 | 5 |
| Promoted improvements or quality in health care  | 1 | 2 | 3 | 4 | 5 |
| Was scientifically rigorous and evidence-based   | 1 | 2 | 3 | 4 | 5 |
| Avoided commercial bias or influence   | 1 | 2 | 3 | 4 | 5 |
| Provided appropriate and effective opportunities for active learning<br>(e.g., case studies, discussion, Q&A, etc) | 1 | 2 | 3 | 4 | 5 |
| My opportunity for learning assessment was appropriate to the activity   | 1 | 2 | 3 | 4 | 5 |

**Handout materials were useful:**  Yes     No     No handouts for this activity

**Would you be willing to participate in a post-activity follow-up survey?**  Yes     No

**Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:**

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at [www.cmeuniversity.com](http://www.cmeuniversity.com). On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 8647**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

**Post-test Answer Key**

1	2	3	4	5	6	7	8	9	10

**Request for Credit (\*required fields)**

Name\* \_\_\_\_\_ Degree\* \_\_\_\_\_

Organization \_\_\_\_\_ Specialty\* \_\_\_\_\_

City, State, ZIP\* \_\_\_\_\_

Telephone \_\_\_\_\_ Fax \_\_\_\_\_ Email\* \_\_\_\_\_

Signature\* \_\_\_\_\_ Date\* \_\_\_\_\_

**For Physicians Only:** I certify my actual time spent to complete this educational activity to be:

- I participated in the entire activity and claim 1.0 credits.
- I participated in only part of the activity and claim \_\_\_\_\_ credits.