

# ASH 2006 Multiple Myeloma Highlights for Physicians

*Highlights from the 48th Annual Meeting of the  
American Society for Hematology (ASH) held in  
Orlando Florida, December 9–12, 2006*

by Lynne Lederman, PhD





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## A Changing Landscape

The 48<sup>th</sup> Annual Meeting of the American Society for Hematology (ASH) was held December 9<sup>th</sup> through 12<sup>th</sup>, 2006, in Orlando, Florida. There were at least 10 simultaneous sessions that included oral presentations of studies related to multiple myeloma, as well as about 200 myeloma-related posters. In addition, the International Myeloma Foundation sponsored a Satellite Symposium on Innovative Strategies for Treating Myeloma: Case Discussions, on December 8<sup>th</sup>. There was also an Education Program on multiple myeloma and a Scientific Committee Session on growth factor networks in myeloma bone disease.

The landscape of multiple myeloma treatment continues to evolve as research results accumulate from trials of conventional and new therapies and from studies on risk factors and side effects.

## Bank on a Cure<sup>®</sup> (BOAC) Gene Bank Research Presented

### Survival-Associated Genes

Brian Van Ness, University of Minnesota, used the BOAC single nucleotide polymorphism (SNP) chip to look for SNPs associated with event-free survival in patients in two large Phase III clinical trials, EGOG E9486 and SWOG S9321 (abstract # 131). The BOAC SNP chip contains 3,404 SNPs associated with gene functions that are expected to influence disease progression and response to therapy, including networks involved in drug metabolism, bone microenvironment, immune responses, and DNA repair. DNA from patients receiving a variety of regimens will be compared with DNA from healthy subjects. One goal of the SNP analysis is to determine associations with survival, toxicities, bone disease, and age at onset of myeloma. [Preliminary results show that there is a higher rate of variation between racial groups, e.g., white versus black individuals, than within racial groups, e.g., two different groups of white individuals. Therefore, the larger data set of white individuals will be analyzed *first* while additional samples from other groups are obtained.] In the above clinical trials, the top two networks of significant SNP association with survival were DNA repair and immune response. Future analyses include looking at the impact of genetic variation on bone disease.

### Thromboembolic Event-Associated Genes

In a study reported by Gareth Morgan, Institute of Cancer Research, Royal Marsden Hospital, London, (abstract #246), the BOAC team sought to identify factors that might explain why patients treated with thalidomide have a higher rate of venous thromboembolic events (VTE), including deep vein thrombosis (DVT) and pulmonary emboli (PE), than patients treated with other anti-myeloma drugs. VTE can cause considerable disability, even death. The study identified gene clusters associated with VTE by comparing patients treated with thalidomide experiencing VTE with those treated with thalidomide who did not experience VTE. The BOAC SNP chip mentioned above was used to identify genes associated with VTE risk, which included drug metabolism, inflammation, and DNA repair genes. Although the group looked hard for variations in genes associated with blood coagulation, these were not associated with increased VTE risk. Future work will focus on developing a model to predict VTE risk as well as treatment response for individual patients, so that appropriate therapy can be given. The involvement of inflammation in the clotting process explains in part how aspirin can be effective in preventing VTE, although it raises the question of why thalidomide, as an immunomodulatory drug (IMiD), is associated with increased risk of VTE. The risk for thalidomide might be related to rapid breakdown of myeloma cells releasing factors that promote clotting via inflammation.

### Prevention, Identification, and Treatment of Thromboembolic Events

As discussed above, thromboembolic events (TE) include DVT and PE. Jeffrey Zonder, Wayne State University School of Medicine. Some treatments for myeloma, which are associated with an increased risk of TE, including VAD (vincristine, Adriamycin, dexamethasone) due to the use of catheters to deliver the drug combination, as well as to the effects of the drugs themselves, such as Adriamycin (doxorubicin), pegylated liposomal doxorubicin (PLD or Doxil), high-dose dexamethasone, lenalidomide (Revlimid), and, as noted, thalidomide. Patients at higher risk for TE include those with decreased mobility, compression of blood vessels by tumors, or an inherited clotting disorder.

## Treatment-Associated Risks

Although some studies have implicated the use of erythropoietin as a risk factor for TE, Maurizio Zangari, University of Arkansas, presented a poster (abstract #3572) concluding that patients receiving total therapy II (TTII) who also received erythropoietin did not have an increase in venous thromboembolic events. [However, this may have related to the fact that the risk was already high with this multi-drug regimen.] Nor did the use of bortezomib in combination with high-dose dexamethasone and erythropoietin result in increased risk of TE, as presented in a poster by Jean-Luc Harousseau, Hopital Hotel-Dieu, Nantes, France (abstract #3543). In the latter analysis, patients had relapsed myeloma, and it is known that TE is more likely to occur in newly diagnosed myeloma.

Some combinations of drugs, such as high-dose dexamethasone in combination with thalidomide or lenalidomide, may increase the risk of TE, whereas others may not. In an oral presentation, Paul Richardson, Dana-Farber Cancer Institute, noted that in a phase 1 trial of lenalidomide plus bortezomib (abstract #405) in 38 patients with relapsed and/or refractory myeloma, the only TE, a DVT, occurred in a patient who was receiving lenalidomide without bortezomib at the time, along with the anticoagulant low molecular-weight heparin (LMWH).

## TE Prophylaxis

Prevention of TE is important, as is recognizing an event if it occurs, followed by prompt treatment. Preventative treatment may be determined by the individual physician; patient preference and health factors; hospital policy; or reimbursement issues. In the multiple myeloma education session, various treatments to prevent TE were discussed, including full-dose aspirin, full-dose warfarin, or therapeutic doses of LMWH. Aspirin was suggested for patients who were adherent to therapy and were at low risk for TE. There was no agreement on how long to give anticoagulant therapy once an event occurs.

Brian Durie presented a poster (abstract #3571) summarizing recommendations for therapy based on a survey of members of the International Myeloma Working Group (IMWG). Of 67 IMWG members contacted, 23 responded to a survey about DVT. Concerns about DVT did not prevent them from using thalidomide or lenalidomide. Aspirin, either full dose (325 milligrams) or “baby” aspirin (81 milligrams) was preferred to prevent DVT when necessary. When doxorubicin or PLD were added to treatment, increasing the risk for

DVT, there was a preference for warfarin or LMWH. Most felt that the use of thalidomide or lenalidomide as single agents, or use of VAD, MP, bortezomib, or bortezomib with dexamethasone, did not require therapy to prevent DVT. After the occurrence of TE, most IMWG members felt that anti-myeloma therapy could be resumed following appropriate anticoagulant treatment.

IMWG members felt that TE prevention should be studied in clinical trials. There are clinical trials underway to further define prevention of TE, including the ECOG study comparing aspirin to warfarin in patients treated with lenalidomide plus high-dose dexamethasone.

## Bone-related Events including Osteonecrosis of the Jaw

Gregory Mundy, Vanderbilt University, commented during the Scientific Committee Session that “myeloma bone disease is unique. We are still guessing about the molecular mechanisms for targeted therapy. As bone involvement is altered, we may alter the natural history of the disease.” Improved imaging techniques have shown bone involvement in myeloma to be more common than previously thought. The use of bisphosphonates has resulted in significant decreases in the incidence of skeletal-related events and abnormally high levels of calcium in the blood. However, side effects such as osteonecrosis of the jaw (ONJ) are appearing with the long-term use of bisphosphonates and the development of more active bisphosphonates.

In the education session, Bhoomi Mehrotra, Long Island Jewish Medical Center, pointed out that most of the studies on ONJ have been retrospective, and there have been no basic science studies on how the condition develops, although it has been known for over 150 years to be associated with exposure to phosphorus (the “phospho” in bisphosphonates). The rate of ONJ in both retrospective and prospective studies in patients with myeloma varies from less than 2% to over 12%. The incidence increases with length of time of exposure and the strength of the bisphosphonate. Risk factors include dental disease and surgical procedures. ONJ may be prevented by completing dental work prior to therapy and by avoiding invasive dental procedures while taking bisphosphonates. There was no consensus on what to do if dental surgery is necessary while a patient was taking bisphosphonates, the length of time of return of function after stopping bisphosphonate therapy, or the duration of bisphosphonate therapy needed. Future trials may answer some of these questions.

## **New Treatment Options Change Risk Profiles**

Staging systems for myeloma are based on factors that are related to survival duration. Patients with shorter survival may require different therapies. However, as new treatments, particularly novel and targeted therapies, are developed, factors previously associated with high-risk disease may no longer confer the same level of risk. Although chromosome 13 deletion [del (13)] has been identified as a risk factor, bortezomib treatment overcomes this risk. Preliminary data of the MM016 trial were presented in a poster (abstract #3557) by Nizar Bahlis which suggest that lenalidomide, which was administered with dexamethasone, can also overcome the poor prognosis conferred by del (13) as well as by translocation (4;14). Only 42 patients were treated in this trial. Although differences in response rates and event-free survival between groups of patients with and without these cytogenetic abnormalities are not statistically significant, longer follow-up is necessary to determine whether lenalidomide plus dexamethasone will improve overall survival in patients with high-risk disease.

John Shaughnessy, University of Arkansas for Medical Sciences, presented an analysis of gene expression in tumor cells from 532 patients with newly diagnosed myeloma treated with total therapy (TT) 2 or 3 in order to identify those genes associated with an increase risk (abstract #111). His group identified 70 genes, almost a third of which mapped to chromosome 1, particularly a region known as 1q21. A high rate of tumor cell proliferation and resistance are associated with overexpression of genes in 1q; additional loss of genes in another region of chromosome 1, region 1p, also increases risk. In a poster (abstract #3396), Johannes Drach, Medical University of Vienna, Austria, also showed that amplification of 1q21 as determined by FISH (fluorescent in situ hybridization) was associated with poor outcome after treatment with bortezomib in 46 patients with relapsed and/or refractory myeloma.

## **Trial Results in Patients with Newly-diagnosed Myeloma**

### **IMiD-Containing Regimens**

Vincent Rajkumar, Mayo Clinic, presented results of the MM003 randomized, double-blind, placebo-controlled trial of thalidomide plus dexamethasone in 470 patients with newly diagnosed myeloma (abstract #795). Patients treated with thalidomide plus dexamethasone had a significantly longer time to disease progression, 22.4 months versus

6.5 months with dex alone. Complete response (CR) rates were 7.7% for the combination compared with 2.6% for dexamethasone; partial response (PR) rates were 55.3% and 43.4%, respectively, by EBMT criteria, which was statistically significant. By IMWG criteria, overall responses were also significantly better for the combination. In patients receiving thalidomide plus dexamethasone, the rate of DVT was 18% compared with 4% in patients receiving dexamethasone alone, and although routine prophylaxis was not used in the trial, Dr. Rajkumar believes it is justified in patients receiving the combination. The combination was reasonably well tolerated, and neuropathy although not severe, was common and required monitoring and dose adjustment.

Dr. Rajkumar also presented the results of the ECOG E4A03 randomized Phase III trial of lenalidomide plus high-dose dexamethasone compared with lenalidomide plus low-dose dexamethasone in 445 patients with newly diagnosed myeloma (abstract #799). One aim was to see if efficacy could be maintained with increased safety by lowering the dexamethasone dose. Initially, DVT prophylaxis with aspirin was recommended but not required. However, after the first 4 months, due to an 18% rate of DVT in the high-dose dexamethasone arm, patients enrolled after that point in the trial were required to take aspirin, and the use of warfarin or LMWH was strongly recommended for patients in that arm of the trial. The Independent Data Monitoring Committee has released some of the early safety results, but the efficacy results of this trial are not yet available. It appears that lowering the dose of dexamethasone in combination with lenalidomide results in decreased toxicity, and that all patients should receive DVT prophylaxis. An expansion of this trial will compare patients randomized to lenalidomide plus high-dose dexamethasone and either aspirin or warfarin for 4 months followed by aspirin.

Antonio Palumbo, Division of Hematology, University of Torino, Italy, presented the results of a Phase I/II trial of R-MP–lenalidomide (5 or 10 mg daily) plus melphalan (0.18 to 0.25 mg/kg days 1 through 4) and prednisone (2 mg/kg days 1 through 4) (R-MP) in 53 newly diagnosed patients (abstract #800). Patients received 100 mg aspirin per day and DVT occurred in 2 patients after discontinuation of aspirin. Compared with historic data of treatment with thalidomide plus melphalan and prednisone, treatment resulted in earlier and increased response rates, particularly with the higher doses of lenalidomide and/or MP, as well as longer event-free survival. DLT (dose-limiting toxicity) included neutropenia, neutropenic fever, and treatment delay. The

MM-015 trial will compare R-MP followed by lenalidomide maintenance vs. R-MP or MP with no maintenance.

### **Bortezomib-Containing Regimens**

Dr. Orłowski presented the results of CALGB Phase II trial 10301 of combination bortezomib and the anthracycline pegylated liposomal doxorubicin (PLD, or Doxil) in 63 patients with newly diagnosed myeloma (abstract #797). As a steroid-free regimen, this combination shows promising activity and allows collection of stem cells for autologous transplant. The CR/near CR (nCR) rate was 28%, with an overall response rate of 79%. Time to progression was 9.3 months, significantly longer than the 3.8 months seen on prior therapy. There were no incidents of DVT or PE and no prophylaxis was used. Fatigue, sensory neuropathy, hand-foot syndrome, and syncope were the most common non-hematologic AE.

Sundar Jagannath reported on the extended follow-up of a Phase II trial of bortezomib alone and in combination with dexamethasone in the frontline setting (abstract #796). Of 49 patients enrolled, 13 received bortezomib alone, and 36 received the combination. The overall response rate was 90%; 38% of patients had CR or VGPR. The addition of dexamethasone improved response in 72% of patients. The one-year survival rate is 90%. The AE were predictable and manageable, with the most common grade 2 or higher AE being sensory neuropathy or neuropathic pain, fatigue, constipation, nausea, and neutropenia. Two grade 4 events, neutropenia and thrombocytopenia, were observed. Combination bortezomib plus dexamethasone does not compromise hematopoietic stem cell collection or engraftment. A Phase III trial, IFM 2005-1, comparing bortezomib plus dexamethasone with VAD as induction therapy prior to high-dose therapy with stem cell transplant is ongoing (see next paragraph).

Jean-Luc Harousseau, Hopital Hotel-Dieu, Nantes, France, presented preliminary results of the IFM 2005-01 randomized, multicenter, Phase III trial of bortezomib plus dexamethasone versus VAD as induction therapy prior to autologous stem cell transplantation in newly diagnosed patients with myeloma (abstract #56). Patients were randomized to induction therapy with 4 cycles of either VAD or bortezomib plus dexamethasone. Half of each of these groups also received DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin) as consolidation therapy. After MEL200 and transplant, patients who did not have CR/VGPR could receive a second transplant. Data are available for the first 165 of 420 patients enrolled. The overall

response was 67% in all 82 patients receiving VAD and 82% in all 79 patients receiving bortezomib plus dexamethasone. DCEP increased the overall response rate from 79% to 89%. The toxicity profiles were similar, with a higher rate of grade 3-4 mucositis in patients treated with VAD, and a higher rate of neuropathy in patients treated with bortezomib plus dexamethasone. Accrual is nearly complete.

Andrzej J. Jakubowiak presented the results of initial therapy with bortezomib, PLD, and dexamethasone in 36 patients (abstract #3093). Of 28 evaluable patients, the overall response was 89%, with 32% CR/nCR and 21% VGPR. The treatment did not interfere with the collection of stem cells, and post autologous stem cell transplant, the overall response rate increased to 96%. The treatment was well tolerated.

### **Trial Results in Patients with Relapsed and/or Refractory Myeloma**

#### **Bortezomib-Containing Regimens**

Dr. Orłowski also presented the results of a planned interim analysis of a Phase III trial (DOXIL-MMY-3001) of combination bortezomib and PLD in 646 patients with relapsed/refractory myeloma (abstract #404). This combination resulted in significant increases in time to disease progression (9.3 months) and duration of response (10.2 months) compared with bortezomib alone (6.5 months and 7.0 months, respectively). There was no significant difference in overall survival or overall response, which was 43% for bortezomib alone (n=310) and 48% for the combination (n=303). Subgroup analyses indicated that the combination was more effective in patients regardless of age, sex, beta-2-microglobulin levels, prior treatment, performance status, prior stem cell transplant, prior anthracycline or IMiD use, or presence of cytogenetic abnormalities. Toxicity was predictable and manageable, and incidence of TE was low. A pharmacoeconomic analysis is being performed to determine the cost of increasing the duration of response by 3 months for the drug combination.

Ruben Niesvizky, Weill Cornell Medical College, presented an updated analysis of response and time-to-event data from the Phase II SUMMIT and Phase III APEX trials of bortezomib with and without dexamethasone in patients with relapsed/refractory myeloma (abstract #3529). A better quality of response was associated with better clinical benefit in terms of extended treatment-free interval, time to alternative therapy, and time to progression. The authors conclude that CR and nCR are surrogate markers for these clinical benefits in

patients with relapsed and refractory myeloma, and may be related to increased overall survival in some patients.

Joseph Mikhael, Princess Margaret Hospital, Toronto, presented preliminary safety and efficacy results from an international Phase IIIb study that allowed expanded access to bortezomib for patients with relapsed/refractory myeloma who had been treated with at least 2 prior lines of therapy and required therapy for relapsed or progressive disease (abstract #3530). This study enrolled 624 patients who received bortezomib per standard dose and schedule; dexamethasone was added if there was progressive disease (PD) after cycle 2 or stable disease (SD) after cycle 4. The safety profile was similar to that seen in previous Phase II and III trials. PR occurred in 54% of patients, median time to first response was 42 days, and median time to best response was 63 days.

Jeffrey Lee Wolf, Alta Bates Comprehensive Cancer Center, Berkeley, California, presented results of a retrospective review of bortezomib treatment and retreatment in 22 patients who had received the drug in clinical trials (abstract #3532). The 50% response rate seen upon retreatment did not depend on the use of combination therapy. Higher response rates (75%) upon retreatment were seen in patients who had a treatment-free interval of greater than 6 months, compared with a 25% response rate in patients with a treatment-free interval of less than 6 months. Treatment duration was 4.9 months.

Natalie S. Callander, University of Wisconsin, Madison, presented the results of a Phase II trial of bortezomib combined with weekly doxorubicin and dexamethasone in patients with relapsed or refractory myeloma (abstract #3545). Prophylactic acyclovir was required. The overall response in 12 evaluable patients was 83%, with a median time to response of 6 weeks. One grade 4 AE, infection, was observed. Grade 3 AE included thrombocytopenia, anemia, infection, neuropathy, DVT, and neutropenic fever. In myeloma cells isolated from patients, there were various levels of NF-kappa B activity, and the activity was inhibited by treatment in only one of the 5 patients whose cells were examined in vitro. Data were not sufficient to correlate bortezomib-induced NF-kappa B activity with clinical response in this study.

Brian A. Di Carlo, Weill Cornell Medical College, discussed the results of a Phase II pilot study designed to determine if the addition of liposomal doxorubicin (PLD) to therapy with bortezomib and dexamethasone could improve the response in 11 patients with previously treated myeloma

whose disease shows a plateau of M-protein response (abstract #3538). Plateau was defined as less than a 25% change in M-protein over three measurements. Patients received 6 cycles of bortezomib and dexamethasone with PLD added for suboptimal response. The combination of all three drugs appears to be well tolerated, with expected toxicities associated with high-dose dexamethasone. Hand/foot syndrome occurred in 2 patients, requiring discontinuation of PLD in one. The combination appeared to reduce tumor burden and warrants further study. In a related poster (abstract #2953), Jessica L. Stern reported that this regimen, followed by bortezomib plus high-dose cyclophosphamide and G-CSF, allowed collection of a high number of hematopoietic stem cells in a short time period.

Donna E. Reece, Princess Margaret Hospital, presented the results of a Phase I/II trial of bortezomib plus oral cyclophosphamide and prednisone in patients with relapsed/refractory myeloma (abstract #3536). There were 37 patients enrolled in this open-label, dose-finding study. Bortezomib 1.3 mg/m<sup>2</sup> on days 1, 4, 8, and 11 or 1.5 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day cycle can be added to full doses of cyclophosphamide plus alternate-day prednisone. An overall response rate of up to 84% was seen with the higher bortezomib dose at weekly intervals with excellent tolerability and no significant neurotoxicity. At the lower, more frequent dose, thrombocytopenia occurred more frequently. The incidence of shingles was 30%, therefore, prophylaxis is recommended. The authors conclude that progression-free survival and overall survival compare favorably to other combination regimens.

### **IMiD-Containing Regimens**

Stefan Knop, University Hospital, Wuerzburg, Germany, presented preliminary results of a Phase I/II trial of lenalidomide, Adriamycin, and dexamethasone in patients with relapsed myeloma. Patients were required to take 100 mg of aspirin daily to prevent DVT. In Phase I, 24 patients were enrolled; in Phase II, 34 additional patients were enrolled. The trial established doses of 25 mg lenalidomide daily, 9 mg/m<sup>2</sup> Adriamycin days 1 through 4, and 40 mg dexamethasone days 1 through 4 and 17 through 20 of a 21-day cycle. Patients also received pegfilgrastim. The overall response rate was 84% in 37 evaluable patients.

### **Bortezomib Plus IMiD Regimens**

Paul Richardson, Dana-Farber Cancer Institute, Boston, Massachusetts, presented the final results of a dose escalation, Phase I trial of lenalidomide plus bortezomib

(abstract #405) in 38 patients with relapsed and/or refractory myeloma. The combination was well tolerated and resulted in a 58% response rate in 36 evaluable patients. The MTD (maximum tolerated dose) was defined at 15 mg/day lenalidomide plus 1.0 mg/m<sup>2</sup> bortezomib on the standard 21-day cycle. Initially no anticoagulation was required, but the protocol was later amended to include 325 mg/day aspirin. Although 15 patients also received dexamethasone, the lenalidomide plus bortezomib combination offers a “steroid sparing” approach, and Phase II trials are ongoing in patients with newly diagnosed myeloma as well as in the relapsed and refractory setting.

Dr. Palumbo also presented the results of a Phase I/II dose escalation trial of bortezomib, melphalan, prednisone, and thalidomide (VMPT) in patients with relapsed myeloma (abstract #407). DLT included anemia, thrombocytopenia, infections, vasculitis, fatigue, and peripheral neuropathy. There was a 43% CR/VGPR rate in the 30 patients enrolled, compared with a 12% VGPR (0 CR) rate in historic controls treated with MPT. The overall response rate was 100% in patients receiving VMPT as their second line of therapy. Progression-free survival at 12 months was 61% and overall survival was 84%. A trial of VMPT with bortezomib plus thalidomide maintenance compared with VMP and no maintenance is planned.

Asher Alban Chanan-Khan presented the final results of a Phase II trial of bortezomib in combination with PLD and thalidomide in patients with relapsed or refractory myeloma (abstract #3539). The 23 patients enrolled received 1.3 mg/m<sup>2</sup> bortezomib on days 1, 4, 15, and 18 plus 20 mg/m<sup>2</sup> PLD on days 1 and 15, plus 200 mg daily thalidomide in a 28-day cycle. Low-dose coumadin was used for prevention of VTE. The overall response rate in 18 evaluable patients was 83% (22% CR), with a median progression-free survival of 10.9 months and a median overall survival of 15.7 months. Toxicities included grade 2 palmar-plantar erythrodysesthesia (hand-foot syndrome) in 2 patients, and grade 3 cellulitis in one patient. No VTE occurred. There were no significant grade 3-4 toxicities, cardiotoxicities, or neuropathies.

## **The Standard of Care Continues to Evolve**

### **IMF Satellite Symposium**

The case discussions presented at the Satellite Symposium, chaired by Dr. Durie, demonstrated that practitioners were able to change their treatment concepts of specific patients based on information provided by the panelists: Bart Barlogie, University of Arkansas for Medical Sciences;

Mario Boccadoro, University of Turin, Italy; Dr. Harousseau; Dr. Rajkumar; and Dr. Jesus San-Miguel, University of Salamanca, Spain. Dr. Rajkumar expressed the opinion that VAD was no longer a therapeutically valid option, and that thalidomide plus dexamethasone, bortezomib, or lenalidomide plus dexamethasone offered better response rates. Dr. San Miguel suggested that for newly diagnosed patients, including elderly patients, MP with bortezomib, thalidomide, or lenalidomide were acceptable options, and that the three novel therapies were challenging MP as a standard of care.

Dr. Barlogie gave his opinion that the use of CR as a surrogate marker for outcome is important only for the 20% or so of patients who have been identified as high risk by gene expression analysis, whereas Dr. Boccadoro expressed the opinion that CR is a marker for prolonged survival in all patient subgroups. Both Drs. Harousseau and Boccadoro believe that tandem autologous transplants plus one of the new agents are appropriate in younger patients, but that a single autologous transplant may be sufficient if a CR is achieved. For high-risk patients, Dr. Rajkumar believes that the routine use of autologous stem cell transplantation cannot be justified and that bortezomib should be used up front for these patients. Dr. Barlogie recommends the use of TT3, which includes not only intense drug therapy and tandem transplants, but also a maintenance phase. However, the benefits of maintenance therapy as well as the best maintenance regimen remain to be determined by further trials. Important issues include improvement of patient quality of life and consideration of the cost and convenience of therapy. The participants were asked at the end of the symposium which of the new agents or combinations currently in clinical trial they thought would most likely enter clinical practice. The three most popular answers were bortezomib plus lenalidomide, new proteasome inhibitors, and bortezomib plus the HSP-90 inhibitor KOS-953, which is discussed below.

### **Multiple Myeloma Education Session**

In the multiple myeloma education session, Robert Orłowski, University of North Carolina Chapel Hill School of Medicine, concluded that melphalan plus prednisone (MP) should no longer be considered the standard of care for all patients who are not stem cell transplant candidates. Rather, MP plus thalidomide (MPT) should be considered because it prolongs survival. Because MPT is associated with increased toxicity, MP may be a better choice for patients with poorer organ function. Dr. Orłowski finds RMP [MP plus lenalidomide (Revlimid)] and MPV [MP plus bortezomib (Velcade)]

attractive as well. A Phase III trial comparing MPT with RMP is planned and one comparing MPV with MP is ongoing.

## **New Treatments on the Horizon**

As the natural history of myeloma is better understood, new therapies can be designed to target specific pathways involved in the disease. For example, it is known that interaction of myeloma cells with the bone marrow microenvironment is of central importance. New agents are being developed to block adherence of myeloma cells to stromal cells in the bone marrow, which may prevent multiplication of the myeloma cells, development of drug resistance, and occurrence of lytic bone lesions. As proteins essential for the development and progression of myeloma on the surface of myeloma and stromal cells are identified, specific antibodies and vaccines may be developed.

Targeted therapies, that is, drugs designed to attack specific growth factors and other molecules involved in the development and progression of myeloma, will continue to increase the arsenal of available treatments. Many of these therapies will be used in combinations that exploit their activity against different parts of the myeloma cell life-cycle. This

may allow more effective treatment without an increase in side effects.

Interesting clinical trials and preclinical studies are summarized in the two tables on pages 11 and 12.

## **Future Directions**

Patients with myeloma can look forward to continuing development of new treatment options, including novel and targeted therapies, along with improved management of their disease through the use of specific combinations of existing drugs. Gene expression profiling will continue to identify subgroups of patients with higher-risk disease, while at the same time, new therapies may be expected to overcome some, if not all, of these risk factors. Increasingly, physicians are considering not only event-free and overall survival, but patient quality of life and the cost and convenience of treatment, as the therapeutic options for patients with multiple myeloma continue to increase not only in number, but also in efficacy.

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## Clinical Trial Results

<i>Treatment</i>	<i>Author (abstract)</i>	<i>Study Design</i>	<i>Results and Conclusions</i>
<b>Bortezomib</b> in combination with <b>Samarium Sm 153 lexidronam</b> , a bone-seeking radioactive compound	Berenson (#3544)	Phase I, dose-escalation trial, with a goal of increasing efficacy without increasing toxicity. 18 patients with relapsed and refractory myeloma have been enrolled.	The drug combination has been well-tolerated. Responses have been seen in 3 patients and stable disease in 4 patients. Follow-up is continuing and a Phase II study is planned.
<b>ZIO-101</b> , a new organic form of arsenic that can be given at much higher doses than arsenic trioxide	Berenson (#1966)	Phase I trial in patients with previously treated myeloma or acute myelogenous leukemia.	ZIO-101 was well-tolerated, the MTD was determined, and disease was stabilized for over 6 months in one patient with rapidly progressing myeloma resistant to both arsenic trioxide and bortezomib. Phase II trials are on-going.
<b>SCIO-469</b> , an inhibitor of p38a mitogen-activated protein kinase (MAPK), as monotherapy or in combination with <b>bortezomib</b>	Siegal (#3580)	Phase II trial in patients with relapsed refractory myeloma. Of 62 patients enrolled in the trial, 28 patients received SCIO-469 as a single agent (60 mg P.O. tid) and 34 patients received SCIO-469 in combination with bortezomib for PD or SD (1.0 to 1.3 mg/m <sup>2</sup> on the standard schedule).	There were no responses to SCIO-469 as a single agent. There were 12 (35%) PR and 4 (12%) minimal response (MR) among 34 patients receiving the combination (ORR = 47%). The 10 deaths that occurred were due to progressive disease (n=7) or infection (n=3). Both treatments were well tolerated; the most common AE for the combination were fatigue, nausea, peripheral neuropathy (grade 1 or 2), and thrombocytopenia. Further studies to refine the dose of SCIO-469 and to investigate other drug combinations and patient subpopulations were proposed.
<b>Perifosine (KRX-0401)</b> , an oral, novel, synthetic alkylphospholipid that inhibits Akt, alone and with <b>dexamethasone</b>	Richardson (#3582)	Phase II trial in patients with relapsed or relapsed/refractory myeloma. Patients received 150 mg perifosine daily. Dose reduction to 100 mg was required in 12 patients, and to 50 mg in 4 patients.	Of 55 patients enrolled, 33 were evaluable for response, and best response, SD, was seen in 13 patients for a median duration of 12 weeks. Of 23 evaluable patients who received dexamethasone, there were 2 (9%) PR, 4 (17%) MR, and 11 (48%) SD. The most common AE were nausea, vomiting, diarrhea, fatigue, and increased creatinine. Further studies are expected to evaluate other dosing schedules and combinations with other agents, including bortezomib and lenalidomide.
<b>Histone Deacetylase (HDAC) Inhibitors</b>			
<b>PXD-101</b> alone and in combination with <b>dexamethasone</b>	Sullivan (#3583)	Phase II trial of PXD-101 with dexamethasone (if PD) in 25 patients with advanced myeloma; 900 to 1000 mg/m <sup>2</sup> as a 30 minute I.V. infusion on days 1 through 5 of a 21-day cycle	PXD-101 was well-tolerated. There were no objective responses to the single agent, with SD in about 40% of patients. Of 8 patients who received the combination, there were 2 PR, 2 MR, and 4 SD. Trials of PXD-101 in combination with bortezomib are planned.

## Clinical Trial Results (continued)

<i>Treatment</i>	<i>Author (abstract)</i>	<i>Study Design</i>	<i>Results and Conclusions</i>
<b>Heat Shock Protein (HSP) Inhibitors</b>			
<b>Tanespimycin (17-AAG; KOS-953)</b> , a HSP-90 inhibitor in combination with <b>bortezomib</b>	Richardson (#406)	Phase I trial in 30 heavily pretreated patients with relapsed/refractory myeloma.	Toxicities were expected and manageable. The overall response rate was 57% in 23 evaluable patients, including patients who were pretreated with or refractory to bortezomib. No MTD was defined and dose escalation is continuing. Sufficient responses were seen to justify a Phase III trial in patients at first relapse and with multiple prior therapies.
<b>IPI-504</b> , a water-soluble HSP-90 inhibitor	Siegel (#3579)	Update of Phase I clinical trial in 18 patients with relapsed/refractory myeloma. Escalating doses up to 400 mg/m <sup>2</sup> intravenously using the same schedule that is used for bortezomib.	No DLT or drug-related grade 3-4 AE observed. AE were mild and included mild infusion site reactions, musculoskeletal pain, and GI symptoms. Peripheral neuropathy, myelosuppression, DVT, or clinically significant cardiac toxicity were not observed. The MTD was not identified. Of 17 evaluable patients, best response was SD in 3 patients. Further studies are planned.
<b>Stem Cell Mobilizer AMD3100</b>			
<b>AMD3100</b>	Flomenberg (#3381)	AMD3100 without G-CSF to increase the number of hematopoietic stem cells mobilized	Of 9 patients with myeloma enrolled, all patients mobilized sufficient cells, in 3 days in 1 patient and 4 days in 8 patients. All received transplants. AMD3100 was generally well tolerated and engraftment occurred in about 10 days. More cells are mobilized with G-CSF, but the population is more primitive. Further evaluation was suggested.
<b>AMD3100 with G-CSF</b>	Douglas (33383)	AMD3100 with G-CSF	There were 11 patients with myeloma in the study. AMD3100 was generally safe and well tolerated and increased stem cell mobilization in patients with myeloma.

## Preclinical Results

<i>Treatment</i>	<i>Author (abstract)</i>	<i>Results and Conclusions</i>
<b>Histone Deacetylase (HDAC) Inhibitors</b>		
<b>PXD-101</b> in combination with <b>bortezomib</b>	Feng (#507)	The combination resulted in significantly greater inhibition of myeloma cell proliferation and viability, induced a higher degree of apoptosis, caspase cleavage, and apoptosis-related gene expression, and more strongly inhibited osteoclast formation in culture than either agent alone. The combination also synergistically suppressed the growth of human myeloma xenografts compared with either agent alone.
<b>Proteasome Inhibitors other than Bortezomib</b>		
<b>PR-171</b> and structurally related, orally bioavailable analogs	Kirk (#3581)	PR-171 analogs are bioavailable after oral dosing and induce proteasome inhibition in mice, in which multiple doses were tolerated. Anti-myeloma activity was seen in mice bearing tumors from myeloma cell lines and human xenografts.
<b>Signal Transduction Modulators</b>		
<b>Perifosine</b> plus <b>TRAIL (TNF-related apoptosis-inducing ligand)</b>	David (#3446)	Synergistic induction of apoptosis in myeloma cell lines. The authors conclude the combination should be investigated in primary myeloma cells, and has clinical potential.

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