

# ASCO 2007 Highlights for Physicians

by Lynne Lederman, PhD





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## New Standards are Emerging: News from the 2007 ASCO Meeting

New and updated data on the use of novel therapeutics in combination therapy in patients with newly diagnosed or relapsed/refractory multiple myeloma were presented at the 2007 meeting of the American Society of Clinical Oncology (ASCO), June 1 through 5, in Chicago, Illinois. Results from the E4A03 ECOG trial of lenalidomide plus either high- or low-dose dexamethasone in newly diagnosed patients demonstrated the advantages of low-dose dexamethasone. Additional data were presented from the DOXIL-MMY-3002 trial of pegylated liposomal doxorubicin (Doxil®) plus bortezomib in patients with relapsed/refractory myeloma who had received at least one prior therapy. In addition, there was an educational session on optimizing the therapy for multiple myeloma; discussions on risk-based approaches to therapy; insights into the natural history of myeloma; updates of other clinical trials; and reports on agents in development.

## Risk-Based Approaches to Therapy

According to Leif Bergsagel (Mayo Clinic, Scottsdale, Arizona), session chair for a discussion of molecular classification of myeloma and the implications for a risk-based approach to therapy,

there have been really exciting advances in understanding the pathogenesis of myeloma and in its treatment. Patients treated today may not be cured, but their survival can be extended so that they will live longer and eventually die of other causes than myeloma. The heterogeneous nature of survival has a genetic basis that is being investigated using a variety of techniques. These include gene expression profiling (GEP) and array comparative genomic hybridization (aCGH) to identify over- and under-expressed genes associated with disease progression, drug resistance, and prognosis. aCGH allows identification of genetic variants that may be enriched over the course of treatment and helps pinpoint progression that would be missed by fluorescent in situ hybridization (FISH) or gene sequencing. Dr. Bergsagel noted that although GEP can be used to define a high-risk

signature, it will be necessary to find a way to translate this into clinical use. In addition, although certain cytogenetic abnormalities or genetic profiles may be used to define a higher-risk population, some therapeutic agents may be able to overcome this risk.

Mutations leading to dysregulation of the canonical (classical) and non-canonical (alternative) NF kappa B pathways are important in myeloma. Some of these may allow myeloma cells to by-pass signals usually provided by interaction with the bone marrow microenvironment. Drugs may interfere with the activity of mutations in one or both pathways, e.g., dexamethasone affects components of the canonical pathway, whereas bortezomib can block both the canonical and non-canonical pathways because the proteasome is involved in both.

## Prediction of Response and Progression in Multiple Myeloma with Serum-Free Light Chains (sFLC)

Rami N. Khoriaty (Cleveland Clinic, Cleveland, Ohio) presented data showing corroboration of the International Myeloma Working Group (IMWG) response criteria [abstract 8047]. In a retrospective review of 89 patients with myeloma, 43 (48%) had abnormal sFLC (greater than 10 mg/dL). Response rates by EBMT criteria were: 4 (5%) CR, 22 (25%) PR, 26 (29%) PD. For patients with sFLC data (n=43) there were: 14 (32%) PR, 18 (42%) PD. The sensitivity and specificity of sFLC assay are quite good, particularly the negative predictive value (92% for response and 95% for progression). sFLC criteria reliably predicts response/PD in patients who have abnormal sFLC. Dr. Orlowski commented that more studies comparing outcomes using the different response criteria (EBMT and IMWG, the latter equating stringent CR with normalization of free light chain data) in a uniformly treated group of patients are needed to further validate the new criteria. One important outcome of this change in criteria is that all of the studies that have used EBMT criteria previously may have different overall and complete response rates when the new IMWG criteria are applied instead.

## **Factors Predictive of Outcome in Relapsed, Refractory Myeloma Treated with Bortezomib, Melphalan, Prednisone, and Thalidomide (VMPT)**

Antonio Palumbo (University of Torino, Turin, Italy) presented results of a phase I/II study of relapsed/refractory myeloma in patients who had received at least one prior line of therapy and received VMPT as salvage therapy (abstract 8048). As second line, 57% of patients had at least VGPR, while 100% had at least MR (36% CR, 21% VGPR, 21% PR, and 21% MR). No response differences were seen based on age, beta-2-Microglobulin, CRP, deletion 13, line of treatment, or bortezomib dosage, but the power of the data is not optimal because it was a phase I/II study. Low response rate was associated with decreased serum albumin. Lower PFS was associated with CRP, third line of treatment, beta-2-Microglobulin, and creatinine, but not with chromosome 13 deletion. These data suggest that combining novel agents that don't overcome poor-risk cytogenetics (e.g., thalidomide in chromosome 13 deletion) with those that do (in this case, bortezomib) may preserve the latter benefit, while still enhancing overall activity. Dr. Orłowski commented that this study validates that the ISS stage remains an important prognostic system even in the era of novel agents. A planned phase III trial of VMPT vs. VMP may answer the question whether post-VMPT relapse will be more resistant and the disease more aggressive.

## **Current Status of Stem Cell Transplantation**

William Bensinger (Fred Hutchinson Cancer Center, Seattle, Washington) discussed the current status of stem cell transplantation (SCT), including the issues of when, how many, and whether they should be allogeneic, autologous, or both. Autologous SCT (ASCT) results in a high response rate and low mortality and demonstrates the impact of complete response (CR) or near (n) CR on survival, but it is still not curative. Double transplant may be beneficial for selected patients, i.e., those who are not in CR or nCR after the first ASCT. It is not clear if SCT is of benefit to patients with CR following chemotherapy. Although there are enough data to show increased survival with ASCT compared with conventional chemotherapy, it is not known if this will hold when ASCT is compared with novel therapies. It is also not known if all CRs are equal and are independent of the treatment leading to the response.

Although conventional allogeneic SCT can result in prolonged survival, the high mortality is unacceptable. Non-ablative allografting may be an alternative, although response rates are low in patients unless there is only minimal disease. Therefore, the best regimen is unknown. Reduced intensity conditioning (RIC) allogeneic SCT is in clinical trial, but results will not be available for several years. In the meantime, ASCT remains the standard of care for transplant-eligible patients. Maintenance therapy may be beneficial for low risk patients but the best agents are unknown. It is also not known if allogeneic transplant can overcome high-risk cytogenetics. Dr. Bergsagel suggested enrolling patients in a trial to determine this.

## **PETHEMA HDT tandem transplant with stem cell support in primary refractory myeloma**

Results of the Spanish PETHEMA/GEM-2000 trial were presented by Joan Bladé (Hospital Clinic, Barcelona, Spain) [abstract 8021]. Two populations with different outcomes were identified. Patients with primary refractory myeloma were most likely to benefit from early high-dose therapy (HDT) and SCT. Patients received VBMCP/VBAD; if resistant, they received BuMEL-140 or MEL-200/ASCT then CVB/ASCT or a mini-allogeneic transplant if there was a compatible donor. Of 81 patients with refractory myeloma, 50 (62%) had stable disease (SD) and 31 (38%) had progressive disease (PD) after induction. After the first autologous transplant, CR rates were low. The second autologous (n=28) or mini-allogeneic (n=9) SCT procedure resulted in 10% CR with autologous vs. 33% CR with mini-allogeneic, the small numbers of patients making statistical analysis difficult. Median overall survival (OS) was 3.7 years for the 81 patients. Patients with SD vs. PD or with chemosensitive disease vs. primary refractory disease had a significantly greater OS and progression-free survival (PFS). If the response to initial chemotherapy is PD, survival is short despite HDT/SCT. Patients with non-responding, non-PD had a similar survival to that of patients with chemosensitive disease. It must be determined if this is due to HDT or to the natural history of a more indolent disease.

## **Outcome after early relapse post-ASCT for myeloma**

Risk factors for early relapse, defined as less than 12 months after ASCT were studied by Syed T. Mahmood (Mayo Clinic, Rochester, Minnesota) [abstract 8022] in a population of 432 patients with newly diagnosed myeloma treated between 1994 and 2005. Patients were divided into two groups based

on time of relapse. Patients had received various initial therapies including dexamethasone (38.5%), VAD (29.9%), thalidomide/dexamethasone (24.8%), and others; 81.3% had undergone conditioning with MEL 200. The only significant differences in baseline characteristics for the group with early relapse (n=94) vs. late or no relapse (n=338) were plasma cell labeling index (PCLI) of at least 1%, refractory disease at transplant, having received more than one induction regimen, abnormal karyotype, and circulating plasma cells at collection.

The rate of OR was similar (96%) but that of CR was much higher in the late vs. early relapse group (18% vs. 43%). Median post ASCT OS in the late relapse group was 75.7 months, vs. 17.6 months in the early group. Median OS from diagnosis in late vs. early relapse was 82.2 months vs. 23.9 months, and median OS from relapse was 39.6 months vs. 7.8 months, all significantly greater for the late relapse group. In a multivariate analysis, the three factors significantly associated with early relapse were more than one induction regimen, a PCLI greater than 1%, and no CR. Prognostic factors for shorter OS post-ASCT included PCLI greater than 1%, beta-2-microglobulin greater than 5.5 mg/dL, and relapse less than 12 months from ASCT. Median OS for patients with relapse before 2002 was 12.5 months, and after 2002, 20.5 months, suggesting the contribution of newer therapies.

Dr. Mahmood concluded that early relapse after ASCT is a novel predictor for poor outcome; patients who have high-risk disease may not be obvious from conventional risk factors; and these patients should be enrolled in clinical trials. He suggested the data he presented can provide a reference baseline for these trials.

### **High-dose Melphalan-Based Autotransplant**

Mauricio Pineda-Roman (University of Arkansas Medical Sciences, Little Rock, Arkansas) presented the Arkansas experience since 1989 in 3077 successive patients treated with at least one MEL auto-SCT of which 1078 received Total Therapy (TT)-1, 2, or 3; 1104 were on studies for previously treated patients, and 895 were off-study (abstract 8043). Patients on protocols were younger, had better disease parameters, and although cytogenetic abnormalities were similar in three groups, there were fewer cases of chromosome 13 deletion and hypodiploidy in TT groups. TT patients had better OS and EFS; TT3 was better than TT2, which was better than TT1. Parameters predicting good outcome in decreasing order were: favorable cytogenetics (no chromosome 13

deletion or hypodiploidy); platelets at least 100,000; beta-2-microglobulin less than 3; CRP less than 6; CR; and ability to do a second SCT. There was a suggestion that OS, EFS, and CR duration is increasing for 2004 to 2006 for patients on non-TT studies compared with the past. However, OS, EFS, and CR duration for patients off-study do not seem to have improved over this period of time. Dr. Robert Z. Orlowski, University of North Carolina, Chapel Hill, North Carolina, who discussed the poster, noted that the data suggests incorporation of novel agents and application of best therapy is improving outcomes. He was concerned that non-protocol patients have not improved, possibly because they were older, had renal insufficiency, or other poor risk factors, and that help is needed for these patients. These data were collected prior to the era of MP-T, MP-R, and MP-V for older patients. Bortezomib and/or lenalidomide may help those with chromosome 13 deletion.

### **Bortezomib Prior To and as Maintenance Therapy After ASCT**

Sagun D. Goyal (Washington University School of Medicine, St. Louis, Missouri) and Robert Z. Orlowski (University of North Carolina) presented long-term follow-up of a phase II study [abstract 8044]. Of 40 patients who received bortezomib at a standard dose and schedule for 2 cycles post-induction before mobilization, and 6 cycles post-ASCT for 4 weeks out of 5; 14/31 (45%) had at least MR (defined as an M-protein reduction of 25% by serum protein electrophoresis and of 50% by urine protein electrophoresis). Stem cell collection and engraftment were normal and 33/38 (89%) had an overall response rate at day 90 to 120 post transplant of 50% or better; with 27/33 (82%) VGPR at end of study. Median PFS was 626 days and median OS was 64.7% at 3 years. 14/33 (42%) developed post-SCT zoster, indicating a need for prophylaxis against zoster. Dr. Orlowski suggested that randomized studies are needed to support the efficacy of maintenance therapy.

### **Benefit of Reduced Intensity Conditioning (RIC) Allogeneic SCT as Salvage Treatment for Relapsing Myeloma**

Mohamad Mohty (Institute Paoli-Calmettes, Marseille, France) presented results suggesting that for the minority of patients with a matched sibling donor, RIC allo-SCT is a viable option (abstract 8045). Of 32 patients with relapsed/refractory myeloma, 13 did not have allogeneic-matched donors whereas 18 received RIC allo-SCT. Of those without donors 11/13 had PD despite salvage, more chemotherapy,

and another auto-SCT; 6 (46%) were alive, of whom 5 had PD, and PFS was 8% at a median follow-up of 36 months. For patients with donors, 10/18 (56%) were alive with 11/18 responders (4 CR, 5 PR/VGPR) and 5 PD post-SCT; PFS was 46% ( $p=0.01$  vs. the non-alloSCT group). Transplant-related mortality was too high at 33%.

## Treatment Options for Patients with Newly Diagnosed Myeloma

### Late-Breaking Abstract on the E4A03 ECOG Trial

S. Vincent Rajkumar (Mayo Clinic, Rochester Minnesota) presented the late-breaking abstract [8025] on the phase III E4A03 ECOG trial of lenalidomide plus high-dose dexamethasone vs. lenalidomide plus low-dose dexamethasone in 445 patients with newly diagnosed myeloma. One goal of this trial was to compare lenalidomide plus high- or low-dose dexamethasone in an effort to reduce adverse events associated with high-dose dexamethasone. Patients in the high-dose dexamethasone group ( $n=223$ ) received the drug according to the usual schedule, with a total dose of 480 mg per cycle; patients in the low-dose group ( $n=222$ ) received 160 mg of dexamethasone per cycle. Before September 15, 2005, thromboprophylaxis with aspirin was recommended but not mandated; after that date it was mandated that patients receive at least aspirin, but warfarin or low-molecular weight heparin (LMWH) was strongly recommended for patients in the high-dose dexamethasone arm. Baseline characteristics of patients in the two treatment groups were similar.

Serious adverse events (SAE) in the two groups were similar, with the following exceptions: neutropenia was higher in the low-dose dexamethasone group (19% vs. 9.7% in the high-dose group); non-hematologic toxicity was significantly higher in the high-dose vs. the lower-dose dexamethasone group, including infections/pneumonia (14.7% vs. 5.1%); DVT/PE (23.8% vs. 9.1%); hyperglycemia (9.7% vs. 6%); and cardiac ischemia (2.8% vs. 0.5%). DVT/PE in the first 4 months occurred in 20% of patients in the high dose group vs. 7% in the low-dose group. Throughout the trial the incidence was 24% vs. 9%. DVT/PE occurred both before and after mandatory prophylaxis, although many patients were already taking some type of anti-thrombotic therapy. Overall grade 3/4 non-hematologic toxicities, overall SAE, and early deaths were significantly lower in the low-dose arm, although they were lower in the high-dose arm than in previous trials of high-dose dexamethasone. Only about

25% of the patients have gone on to stem cell harvest, and yet, stem cells have been collected from over 90% of the total number of patients.

The trial was stopped because the low-dose arm had a better one-year survival: 96% probability of survival vs. 87% in the low-dose arm. Median OS was 23.6 months in the high-dose group and not reached in the low-dose group. One year survival was higher in patients less than 65 years (98% vs. 91%, low-dose vs. high-dose) compared with age 65 years and older (94% vs. 83%, low-dose vs. high-dose). The response rates, time to progression, and PFS assessments are ongoing. Because lenalidomide plus low-dose dexamethasone is associated with significantly superior one-year survival rate and lower toxicity compared with lenalidomide high-dose dexamethasone, Dr. Rajkumar suggested the low-dose dexamethasone regimen could be adopted as front-line therapy for transplant candidates.

### MP-T vs. MP in patients at least 75 years of age with untreated MM – preliminary results of IFM 01-01

Preliminary results of the IFM 01/01 trial, a randomized, double-blind, placebo-controlled trial of melphalan-prednisone-thalidomide (MP-T) vs. MP in patients at least 75 years of age were presented by Cyrille Hulin on behalf of the Inter-groupe Francophone du Myelome (IFM) [abstract 8001]. MP-T is considered standard treatment for patients age 65 and over. Although trials in patients over age 75 are rare, at least 20% of myeloma patients are in this age group. Patients received 12 cycles MP every 6 weeks (melphalan 0.2 mg/kg per day, days 1 through 4, prednisone 2 mg/kg per day, days 1 through 4). No specific anti-thrombotics were planned but patients with a history of thrombosis were excluded. The MP-T group also received 100 mg of thalidomide daily.

At interim analysis in April 2007, 200 patients (100 patients per group) had been enrolled since April 2002; enrollment was stopped at 232 patients. Significantly more patients withdrew from the MP arm due to progression (60% vs. 30%), and significantly more patients withdrew from the MP-T arm due to toxicity (53% vs. 15%), however, 80% of patients were able to tolerate MP-T for up to 6 months and 65% of patients for up to 1 year. Peripheral neuropathy, neutropenia, and depression were significantly more common in the MP-T arm. There were no significant differences between treatment arms for thrombosis, constipation, somnolence, nausea and vomiting, edema, or deaths due to myeloma, toxicity, or other reasons.

The best response to treatment at 12 months was significantly higher with MP-T (61% at least PR vs. 31% with MP; and 23% at least VGPR vs. 8%). Median PFS was significantly higher for MP-T (24.1 months vs. 19 months for MP). Median OS was 33.3 months. Median OS was not reached but estimated to be 45.3 months for MP-T vs. 27.7 months for MP for 200 patients at interim analysis. These data must be confirmed by analysis of all 232 patients. After progression, survival time was 9.8 months for the MP group vs. 9.3 months for the MP-T group, so salvage after failure of MP is possible. MP-T is effective for patients over the age of 75 with newly diagnosed myeloma and is superior to MP in prolonging PFS. Dr. Hulin concluded further that although the toxicity was acceptable, shortening the duration of thalidomide might reduce neurotoxicity and LMWH or aspirin might decrease the risk of thrombosis.

Sagar Lonial (Emory Winship Cancer Institute, Atlanta, Georgia) commented that this was a landmark study in a difficult population that sets the standard for the future and that the age that is considered “old” keeps increasing. He noted that many advances in treatment have been in younger patients. Limitations in older patients include not just resistance to chemotherapy but increased toxicity and the frail nature of the population. Many drugs are effective but must be delivered in a safe way. That the drop-out rate was higher after 3 months suggests the utility of less toxic novel agents, a shorter induction followed by maintenance, or less frequent thalidomide dosing, i.e., every other day.

### **Incorporation of New Agents**

S. Vincent Rajkumar (Mayo Clinic) summarized the treatment of newly diagnosed myeloma, pointing out that whereas the median survival from diagnosis used to be four years, a “dazzling array of options” is increasingly allowing patients to live a normal life with myeloma, and to live long enough that they are more likely to die of other causes. He believes it is important to stratify patients using the Mayo Clinic’s mSMART classification system into high risk (25% of patients) based on deletion 17p, t(4;14), t(14;16), deletion 13, hypodiploidy, and plasma cell labeling index  $\geq 3\%$  vs. standard risk (75% of patients) based on hyperdiploidy, t(11;14), t(6;14) (Mayo Clin Proc 2007;82:323). Then patients should be stratified based on eligibility for transplant; if eligible, they should receive an upfront regimen that would not affect the ability to collect stem cells.

For non-transplant candidates, initial therapy traditionally was MP, but MP with thalidomide, lenalidomide, or bortezo-

mib appears to offer advantages. For transplant candidates, the induction regimen can’t include melphalan because it inhibits stem cell collection. Thalidomide plus dexamethasone appears to be replacing VAD. Dr. Rajkumar noted that hematologists might not be familiar with treating the non-hematologic side effects of this regimen including constipation, neuropathy, and fatigue. Initial therapy with bortezomib plus dexamethasone is another option; the addition of thalidomide to this regimen may increase the response rate. Lenalidomide plus dexamethasone also results in a higher response rate, and as seen in the ECOG E4A03 trial, and lower-dose dexamethasone is associated with decreased toxicity.

For initial treatment of non-transplant candidates, future options include the use lenalidomide, bortezomib, and low-dose dexamethasone (VRd), which will be tested in clinical trials. Other more intensive regimens include CBD, CRd, and liposomal doxorubicin-containing regimens. For patients with high-risk multiple myeloma, data are accumulating that some of the newer therapies may overcome what previously have been thought of as risk factors, e.g., bortezomib overcoming chromosome 13 deletion. Options for patients with high-risk disease include bortezomib for initial treatment and SCT at first relapse; ASCT followed by non-myeloablative SCT in select patients; or a standard-risk treatment algorithm followed by maintenance therapy.

Although Dr. Rajkumar prefers to see physicians treat their patients with myeloma in the context of a clinical trial, the Mayo Clinic’s mSMART offers an off-study algorithm for patients based on eligibility for transplant stratified by disease risk status ([www.msmaart.org](http://www.msmaart.org)). He emphasized the need to determine the cause of acute renal failure, whether light-chain disease, amyloid, an unrelated condition, or hypercalcemia. Acute renal failure due to myeloma may require plasma exchange, biopsy, and aggressive anti-myeloma therapy, e.g., bortezomib plus dexamethasone or thalidomide plus dexamethasone or bortezomib plus dexamethasone plus thalidomide; irreversible renal failure confers a bad prognosis. For patients at high-risk for DVT, including those taking high dose dexamethasone with thalidomide or lenalidomide, erythropoietin, Adriamycin, or doxorubicin, he suggests prophylaxis with warfarin to an INR of 2 to 3 or LMWH; but if no risk factors, e.g. patients taking lenalidomide with low-dose dexamethasone, aspirin might be sufficient because the risk of other anticoagulants might outweigh the risk of DVT.

## The State of Front-line Therapy

Paul Richardson (Dana-Farber Cancer Institute, Boston, Massachusetts) discussed the current state of front-line therapy in myeloma, noting that induction therapy with novel agents has changed the therapeutic paradigm. Traditionally the aim has been CR or PR and optimizing SCT, but SCT may become optional with more effective therapy, which may also improve efficacy in patients who are not transplant candidates. Thalidomide plus dexamethasone is clearly superior to dexamethasone in newly diagnosed patients, although with relatively low CR rates, but with meaningful TTP and OS. However, TE remains an important side effect.

Lenalidomide with dexamethasone improves efficacy and reduces side effects compared with thalidomide plus dexamethasone. The ECOG E4A03 will be a landmark study, although the response data are not yet complete. TE remains a key issue with this regimen and there is an important need to evaluate optimal thrombo-prophylaxis. Who benefits from aspirin remains an important concern. Dr. Richardson said, "Lenalidomide plus low dose dexamethasone constitutes the superior, and I would argue potentially a new standard, for up-front therapy, with a 96% 1-year survival rate being remarkable." Bortezomib therapy results in a solid and robust CR, especially in combination therapies with dexamethasone or Doxil, and the DVT rate with bortezomib plus Doxil is low.

Ongoing phase III trials in newly diagnosed patients include VISTA (bortezomib plus MP vs. MP); MM-015 (lenalidomide plus MP vs. MP) in the non-SCT setting; and IFM (VAD vs. bortezomib plus dexamethasone) and HOVON (VAD vs. PAD) in the SCT setting. Phase III trials that are planned include E1A06 (RMP vs. MPT), IFM 0701 (Rd vs. MPT), S0777 (Rd vs. RVs) in the non-SCT setting, and E1A05 (RVd vs. Vd) in the SCT setting. Dr. Richardson referred to bortezomib plus lenalidomide and low-dose dexamethasone as his personal favorite upfront regimen. He noted that although some of the novel therapeutics in combination have surpassed conventional therapies in efficacy, challenges remain, including side effects, and determining the optimum sequence of therapy remains an area of very active study.

## Novel Agents in Patients with Relapsed Myeloma

### Pegylated Liposomal Doxorubicin (PLD; Doxil) and Bortezomib

Jean-Luc Harousseau presented the results for TTP and OS for the phase III randomized study of PLD plus bortezomib (n=324) vs. bortezomib alone (n=322) in relapsed/refractory myeloma on behalf of the DOXIL-MMY-3001 study investigators (abstract 8002), an update of an interim analysis presented last year at the American Society of Hematology annual conference. TTP for the bortezomib group was 6.5 months, and for the combination it was significantly (45%) improved at 9.3 months. In a subgroup analysis by risk factor, the combination favored all subgroups tested except those with the lowest beta-1-microglobulin and those with chromosome 13 deletion, where there was no difference between treatment arms.

Response rates were significantly higher in the PLD plus bortezomib group (52%) than in the bortezomib alone group (44%), as was the percentage of CR + VGPR (30% vs. 20%; p=.007). The survival curves for the two arms separate after 1 year of follow-up, so OS data are pending. There is a slight increase in adverse events in the combination arm, including gastrointestinal events, thrombocytopenia, and cytopenia, but discontinuations are primarily due to bortezomib discontinuation. Some adverse events in the combination, e.g., stomatitis and hand foot syndrome, are related to Doxil. The incidence of peripheral neuropathy was the same in both arms and was usually mild; febrile neutropenia and hemorrhage were rare despite neutropenia and thrombocytopenia. TE was low (1%) in both arms, and cardiac events were similar in both arms.

PLD plus bortezomib significantly improved TTP and OS in previously treated myeloma compared with bortezomib alone. These benefits were seen in clinically relevant groups e.g., with prior IMiD therapy, post-transplant, high risk, including elevated beta-2-Microglobulin, cytogenetic abnormalities other than deletion 13, and advanced age. Adverse events were predictable and manageable, and peripheral neuropathy and cardiac toxicity were not increased in the combination. TE was low and no prophylaxis was necessary. The combination of Doxil and bortezomib was recently approved for patients with myeloma who have not previously received bortezomib and who have received at least one prior therapy.

Pieter Sonneveld presented the impact of prior thalidomide therapy on the efficacy of PLD plus bortezomib in relapsed/refractory myeloma [abstract 8023] for the DOXIL-MMY-3001 study investigators. This was a pre-specified subgroup analysis of the study updated by Dr. Harousseau. The rationale for this subgroup analysis was a report of possible resistance to lenalidomide in patients previously treated with thalidomide. This analysis assessed the differences in efficacy, represented by time to progression (TTP), OS, and response rates, between treatment groups of patients with and without prior exposure to the IMiDs lenalidomide or thalidomide. Of 646 patients randomized in the trial, 268 had prior IMiD exposure (94% thalidomide, 6% lenalidomide). Of these, 130 patients received PLD plus bortezomib and 138 received bortezomib alone. Of the 378 IMiD-naïve patients, 194 were randomized to the combination and 184 received bortezomib alone.

The TTP was significantly longer in patients with prior IMiD exposure who received PLD plus bortezomib vs. those who received bortezomib alone and was comparable to TTP in patients treated with PLD plus bortezomib who had no prior IMiD exposure. In patients receiving PLD plus bortezomib, the objective response rates were comparable whether or not they had prior IMiD exposure, and OS and duration of response were also similar. There was also no difference in adverse event rates between groups based on prior IMiD exposure. No thromboembolic events (TE) were observed in IMiD exposed group treated with PLD plus bortezomib, although there was 1 grade 3/4 event in an IMiD-naïve patient treated with PLD plus bortezomib. In 126 patients with prior exposure to thalidomide who received lenalidomide plus dexamethasone, there were 14 TE.

Raymond Comenzo, (Sloan-Kettering, New York City, New York), discussed the DOXIL-MMY-3001 results, noting that the PLD formulation results in a slower clearance and long half-life, and although the mechanism is not fully known, the compound is activated intracellularly, leading to free radical formation, active oxygen species, altered cell membranes, DNA strand breaks, immunogenicity, suppression of MAPK phosphatase expression, and activation of NF kappa B (not desirable in myeloma) with a selectivity for tumor cells. He noted that the improvement in TTP with the combination of PLD plus bortezomib is especially important for patients with relapsed disease and those who don't want to take steroids. Both PLD and bortezomib are active broadly in cancer, are synergistic with other agents, and have similar

temporal activity (half life), complementary pathway effects, and selectivity for tumor cells. Dr. Comenzo observed that this is the first of many bortezomib combination trials. Other agents to be tested with bortezomib include inhibitors of HSP90, MAPK/ERK, IGF-1, and PI3K/AKT.

### **Alternating Bortezomib and Dexamethasone**

Laura Rosiñol (Hospital Clinic, Barcelona, Spain) presented the final results of the phase II PETHEMA trial of alternating bortezomib and dexamethasone as an induction regimen prior to ASCT in younger patients [abstract 8024]. The aims of the study were to decrease toxicity and assess M-protein decrease per cycle. The primary endpoints were response rates and kinetics of the response; secondary endpoints included safety, stem cell collection, and post-transplant response. The study enrolled 40 patients with a median age of 54 years. The standard doses of bortezomib and high-dose dexamethasone were given, but bortezomib was administered only for cycles 1, 3, and 5, and dexamethasone was administered only for cycles 2, 4, and 6.

The best ever overall response rate (ORR) was 82.5%; at the end of induction the ORR was 77.5%. Serum M-protein but not urine M-protein decreased significantly from baseline values. Looking at M-protein by cycle, 20 patients responded to bortezomib and dexamethasone, 10 patients responded to dexamethasone only, and 3 patients responded to bortezomib only. Toxicity was low, with no grade 4 toxicities; grade 3 toxicities included neutropenia and skin and liver toxicity, with 1 incidence of grade 2 neuropathy. Stem cell harvest was excellent. Three months after HDT, ORR was 94%, with 33% CR, 22% VGPR, and 33% PR. This alternating approach was questioned, as it might allow a resistant clone to survive, so it is important to see survival to PD results as well as TTP survival data. Dr. Rosiñol responded that the trial is for induction before ASCT, so it is too early to assess survival.

### **Total Therapy 3 (TT3)**

Bart Barlogie (University of Arkansas Medical Sciences, Little Rock, Arkansas) presented the results of a phase II study of TT3 with bortezomib [abstract 8020]. The aim was to increase the CR rate and extend EFS and OS relative to TT2. Induction therapy was reduced from 4 cycles to 2 cycles to increase compliance rates, and patients up to 75 years old were eligible. For the majority of patients the second transplant took place at 6 months and the final consolidation at 12 months from initiation of therapy. The 303 patients

enrolled have been followed for a median of 24 months, at which time OS was 87% and EFS was 84%. Response duration was CR 91%, nCR 80%, and PR 60%. At 24 months, treatment related mortality was 5%, and the post relapse survival was 24%. The condensed time frame resulted in more patients completing the protocol.

Gene expression profiling (GEP) based on a 70-gene model was used to divide patients into high and low risk subgroups. OS, EFS, and CR duration was significantly longer in the low risk group. Once the GEP score was taken into account, FGFR3 t(4;14) did not affect survival. EFS with TT3 was significantly longer than with TT2 in the GEP-defined low and high risk categories; survival was also significantly longer with TT3 than with TT2 for the FGFR3/MMSET subgroup t(4;14), as was duration of CR for the GEP-defined low risk subgroup. One gene the Arkansas group calls micro-environment-associated gene (MAG-1), when down-regulated after a test dose of bortezomib, confers a survival advantage, although this may not be as significant as other risk factors.

## New Insights into the Natural History of Myeloma

### Survival Outcomes Over the Last Thirty Years

Irfan Jawed (University of Washington, Spokane, Washington) presented survival outcomes for myeloma over three decades based on a retrospective study of outcomes from the Surveillance, Epidemiology, and End Results (SEER) 11-Registries from 1973–2003 [abstract 8019]. The purpose of the study was to analyze how patient characteristics, year of diagnosis, and decade of treatment affected OS and cause-specific survival (CSS). The database contains prognostic factors including age, race, sex, age at diagnosis, and year diagnosed with multiple myeloma for 40,538 patients, which is the largest population that has been studied for myeloma survival outcomes.

The estimated median survival for the entire population was 24 months. There was no significant difference in OS by sex. Blacks and other races had significantly longer OS and CSS than whites; younger age at diagnosis was associated with significantly longer OS and CSS than older age; and OS and CSS were significantly longer for patients diagnosed in the most recent decade for which data were available than in prior decades. In a multivariate analysis for OS and CSS endpoints, significant improvements were seen for patients who were female, younger, or diagnosed and treated in

the most recent decade. CSS but not OS was significantly improved for black patients compared with white patients. OS has improved 10% for patients treated in the recent vs. past decades. Some patients have been observed to survive at least 20 years, which may be associated with new treatments and supportive care. Dr. Jawed plans to analyze the effect of biologics, transplantation, and targeted treatment on survival.

## New Therapies in Development

### A New Proteasome Inhibitor

A. Keith Stewart (Mayo Clinic, Scottsdale, Arizona) presented the results of a phase I trial evaluating carfilzomib (PR-171), a new proteasome inhibitor, in patients with hematologic malignancies including myeloma [abstract 8003]. The properties of PR-171 are compared with those of the approved proteasome inhibitor, bortezomib, in the table below.

PR-171	Bortezomib
Keto-epoxide tetrapeptide	Boronic acid dipeptide
Irreversible	Slowly reversible
Highly selective for chymotrypsin-like active site within the proteasome	Inhibits both chymotrypsin-like and caspase-like activities of the proteasome
Highly selective for proteasome N-terminal threonine active sites	Cross-reactivity with serine proteases

Two parallel phase I dose-escalation studies were conducted in patients with myeloma and other hematologic malignancies that were relapsed or refractory after more than 2 prior treatments; prior bortezomib was allowed. The studies tested two dosing schedules, one of which continuously suppressed proteasome activity, the other of which allowed proteasome recovery between doses. Responses were seen with both schedules, with prolonged duration of response in some patients. Pharmacokinetic studies suggest that PK parameters are unlikely to guide dose selection. Pharmacodynamics (chymotrypsin inhibition assay) suggest that 80% proteasome inhibition correlates with response.

PR-171 is well-tolerated and most adverse events were grade 1/2, but 4 patients had grade 2/3 increase in creatinine that was reversible after the first dose.

Reversible 3/4 thrombocytopenia occurred in patients who had grade 2 thrombocytopenia at enrollment, and there was no peripheral neuropathy. Dose-limiting toxicities included febrile neutropenia and thrombocytopenia in the

continuous inhibition trial and thrombocytopenia, hypoxia, and acute renal failure in the recovery dose trial. Phase II doses have been established and studies are beginning in patients with refractory or relapsed myeloma. Dr. Rajkumar commented that the results are similar to those seen in the early bortezomib trials and he hopes this drug follows a similar path, but trials are needed to determine how PR-171 will perform.

### **ZIO-101, An Organic Arsenical**

James R. Berenson (Institute for Myeloma and Bone Cancer Research, West Hollywood, California) presented updated results of on-going phase 1/2 trials of ZIO-101 (Darinaparsin; S-dimethylarsino-glutathione), a novel, organic arsenic, in patients with advanced/progressive myeloma who had received at least 2 prior therapies [abstract 8109]. The potential anti-myeloma effect of Darinaparsin may result from several activities including disruption of mitochondrial function, increased production of reactive oxygen species, modified signal transduction, and anti-angiogenic activity.

A phase I/II study is investigating dosing with 300 mg/m<sup>2</sup> by intravenous infusion once daily for 5 consecutive days every 4 weeks. The phase II portion of this study is determining the preliminary efficacy and safety profile of this schedule. The second phase II study is investigating a dosing schedule of 420 mg/m<sup>2</sup> twice a week every 3 weeks of a 4-week cycle. The purpose of this study is to determine preliminary efficacy and safety.

There have been 14 patients treated on the first schedule; of 10 patients evaluable for response 4 have SD as their best response. Three patients have been treated on the second schedule, with none evaluable so far. Common side effects include vomiting, fatigue, and pain at the site of infusion in patients receiving their treatment through a peripheral line. More serious side effects observed in a small number of patients include decreased blood cell counts, confusion, and dizziness. No clinically important neuropathy, bone marrow toxicity, or cardiotoxicity have been seen so far.

### **New Route of Administration for Bortezomib?**

Phillippe Moreau (University Hospital, Nantes, France) presented results of a prospective comparison of subcutaneous with intravenous administration of bortezomib in patients with multiple myeloma: pharmacokinetics, efficacy, and toxicity [abstract 8046]. Patients with relapsed/refractory myeloma were randomized to the standard dose and

schedule of bortezomib, given either I.V. or S.C. (n=12 each). C<sub>max</sub> (PK) was lower for the S.C. route, but the AUC similar for both routes of administration. E<sub>max</sub> (proteasome inhibition, a pharmacodynamic parameter) was lower with S.C., but not significantly. Response rates were identical for the two routes, with a similar toxicity profile. A larger study is needed to make sure these data are reproducible. Dr. Orłowski commented that subcutaneous bortezomib could increase convenience for patients and providers, and improve quality of life by decreasing the need for clinic visits and possibly the cost of therapy. Larger, randomized studies are needed to determine the response durability. If true, this finding could facilitate outpatient therapy and other applications of bortezomib, such as in a maintenance setting, post-transplant or post-primary or relapsed/refractory therapy.

### **Other Therapies in Development**

Kenneth C. Anderson, Dana-Farber Cancer Institute, discussed proteasome inhibition and other therapeutic strategies in development for myeloma. These include heat shock protein (HSP) 90 inhibition, which has been shown to be synergistic with bortezomib and well-tolerated in phase I/II trials. The HSP90 inhibitor tanespimycin (KOS-953) will be in a phase III trial. He noted that although no peripheral neuropathy has been seen with novel proteasome inhibitor PR-171 (carfilzomib), it may be too early to draw conclusions. NPI-002 (Salinisporamide A) is another proteasome inhibitor that has activity against the trypsin and chymotrypsin-like activities and against caspase and is now in phase I studies. Another potential target in the proteasome pathway is upstream at ubiquitin ligase.

Future directions include using proteasome inhibition alone and in combination in newly diagnosed patients, selecting combination treatments predicated upon preclinical rationale, and targeting protein catabolism with combination therapy that inhibits both the proteasome and aggresome.

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