



## ASH 2010 Summary of Multiple Myeloma Presentations for Physicians

### Introduction

The 52nd Annual Society of Hematology (ASH) Annual Meeting was held December 4th through 7th, 2010, in Orlando, Florida. This report summarizes presentations at the 2010 ASH Annual Meeting, organized by topics rather than by sessions, providing an overview of information on new drugs in development; clinical trial results; treatment by patient characteristics, e.g., transplant eligibility or stage of disease; risk stratification and staging; disease biology including bone disease and use of bisphosphonates; and maintenance therapy. Although maintenance therapy is summarized in its own section, some trials that include maintenance therapy are summarized in more relevant sections, as many trials are now including some kind of continuing treatment for at least some patients.

On December 3, the International Myeloma Foundation (IMF) and the Postgraduate Institute for Medicine sponsored a symposium that presented an overview of the most recent data from clinical trials to allow participants to provide better care for their patients with multiple myeloma. Dr. Brian G.M. Durie introduced the presenters and topics at the symposium. Summaries of these presentations are included under the appropriate headings.

Multiple myeloma was the topic of many presentations at ASH, including the following:

- ✓ Education sessions were held on advances in the basic science of plasma cell disorders and on supportive care in plasma cell dyscrasias.
- ✓ An education session on high risk hematologic diseases included a talk on ultra high-risk myeloma.
- ✓ A scientific session was conducted on therapeutic targeting of the myeloma stem cell.
- ✓ Over a dozen simultaneous oral sessions (comprising about 6 presentations each) were held specifically on myeloma, with many other sessions presenting related information on transplantation, venous thromboembolism, stem cell collection, tumor cell biology, and other topics of interest.
- ✓ Three poster sessions featured hundreds of posters about myeloma and related topics, e.g., transplantation, pharmacoeconomics, and new drugs in development.

### New Drugs in Development

Studies of new drugs in development discussed in this report include:

- Carfilzomib (PX-171), a proteasome inhibitor
- Pomalidomide, an immunomodulatory drug
- Elotuzumab, a monoclonal antibody
- Temsirolimus, an inhibitor of the mammalian target of rapamycin
- PD0332991, an inhibitor of cyclin-dependent kinases

**IMF Symposium: Case Study 5: Novel Agents and Regimens** was presented by Robert Z. Orłowski, MD, PhD, The University of Texas M. D. Anderson Cancer Center, Houston, TX.

Most of the symposium participants agreed that relapsed/refractory myeloma could be defined as progressive disease on or within 60 days of the last treatment. The National Comprehensive Cancer Network (NCCN) practice guidelines for multiple myeloma recommend repeating the primary therapy if relapse occurs at greater than 6 months; there is the most evidence for using bortezomib, bortezomib plus pegylated liposomal doxorubicin (PLD), or lenalidomide plus dexamethasone; other possibilities include bendamustine, bortezomib plus dexamethasone, lenalidomide, high-dose cyclophosphamide alone or with VAD, thalidomide alone or with dexamethasone, dexamethasone alone, DCEP, or DT-PACE. Dr. Orłowski commented that he would prefer to repeat the primary therapy if relapse occurs at 12 months or more. Upcoming promising approaches include the novel single agents carfilzomib and pomalidomide, which are discussed below. New combinations that seem promising that are in trial include bortezomib and lenalidomide in combination with histone deacetylase (HDAC) inhibitors, monoclonal antibodies, proteasome inhibitors, and other agents. It is also possible to add old agents that are new again to prior active regimens, e.g., cyclophosphamide. Agents that have been used previously can be used again in different combinations.

### **Carfilzomib (PX-171): a Proteasome Inhibitor**

Two carfilzomib trials are summarized in Table 1.

**Carfilzomib, Lenalidomide, and Dexamethasone In Newly Diagnosed Multiple Myeloma: Initial Results of Phase I/II MMRC Trial (Abstract 862)** was presented by Andrzej J. Jakubowiak, University of Michigan, Ann Arbor, MI.

**Results of PX-171-003-A1, An Open-Label, Single-Arm, Phase II (Ph 2) Study of Carfilzomib (CFZ) In Patients (pts) with Relapsed and Refractory Multiple Myeloma (MM) (Abstract 985)** David Samuel diCapua Siegel, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ.

**Table 1. Summary of Carfilzomib Studies**

<b>Abstract First Author</b>	<b>Patients Phase Follow-up</b>	<b>Agents and Doses</b>	<b>Side Effects</b>	<b>Responses</b>
<b>Abstract 862</b> A.J. Jakubowiak	newly diagnosed patients phase I: the maximum tolerated dose (MTD); dose-limiting toxicities (DLT), n= 31 (27 evaluable) phase II: to be initiated median F/U 6 months	carfilzomib (C) days 1, 2, 8, 9, 15, and 16; 20 to 27 to 38 mg/m <sup>2</sup> lenalidomide (R): continuously on days 1 to 21; 25 mg per day low-dose dexamethasone (d); (CRd) days 1, 8, 15, and 22 of a 28 day cycles CRd every other week as maintenance	mostly mild; grade 3 to 4 neutropenia infrequent, no fevers or decline in neutrophils with treatment; no emergence of clinically significant peripheral neuropathy (PN)	stringent complete response (sCR)/CR/near (n)CR=55% sCR=22% partial response (PR) or better=96% (100% after 4 cycles) at least very good (VG)PR=83% and CR/nCR=67% after 8 cycles
<b>Abstract 985</b>	patients with	carfilzomib first dose	77% of patients had	A1 responses: overall

D.S. Siegel	progressive disease (PD) after last therapy with $\geq$ prior lines of therapy, including bortezomib (100%) and thalidomide or lenalidomide phase II: A1 n=257 evaluated for response of the 266 patients enrolled and in the safety population	20 mg/m <sup>2</sup> , registration cohort dose was 27 mg/m <sup>2</sup>	pre-existing PN treatment-emergent adverse events (AE) included few grade 3 to 4 hematologic toxicities: neutropenia=10% non-hematologic toxicities: 12% any grade PN and 0.8% grade 3 and 4 PN; most discontinuations due to PD and none to emerging PN 95 deaths on study mostly due to progressive disease (PD); 16% of patients completed all 12 cycles	response rate (ORR)=24%, at least VGPR=5.5% (0.4 % CR), PR=18.7%, minimal response (MR)=10% median progression-free survival (PFS)=3.7 months median overall survival (OS)=15.5 months; median OS not reached in responders duration of response (DOR)=8.3 months in both PR and MR populations clinical benefit (at least MR)=34%
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## Pomalidomide: an Immunomodulatory Drug (IMiD)

Four pomalidomide trials are summarized in Table 2.

### **Pomalidomide Plus Low-Dose Dexamethasone In Myeloma Refractory to Both Bortezomib and Lenalidomide: Comparison of Two Dosing Strategies In Dual-Refractory Disease**

(Abstract 863) was presented by Martha Lacy, MD, Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN.

**A Phase I/II 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** (Abstract 864) was presented by Paul G Richardson, MD, Dana-Farber Cancer Institute, Boston, MA.

**Phase II Study of 2 Modalities of Pomalidomide (CC4047) Plus Low-Dose Dexamethasone as Therapy for Relapsed Multiple Myeloma. IFM 2009-02** (Abstract 859) was presented by Xavier LeLeu, Service des Maladies du Sang, Hôpital Huriez, Lille, France.

**Table 2. Summary of Pomalidomide Studies**

Abstract First Author	Patients Phase Follow-up	Agents and Doses	Side Effects	Responses
Abstract 863 M.Q. Lacy	patients with relapsed myeloma resistant or refractory to both lenalidomide and bortezomib; n=35	pomalidomide 2 mg daily days 1 to 28 (could be escalated to 4 mg if PD) dexamethasone 40 mg	most patients experienced hematologic toxicity; non-hematologic toxicities included	PR or better=26%; MR or better=49%; median time to response (TTR) 1 month; DOR 12

	Phase I/II median F/U 9.1 months	days 1, 8, 15, 22 full-dose aspirin or low-molecular-weight heparin (LMWH) or warfarin	fatigue and PN in most patients; 70% PN at study entry, 20% pomalidomide- related PN during study; 2 instances of deep vein thrombosis (DVT) and 1 myocardial infarction (MI)	months; survival at 6 months=78%; median survival not reached
<b>Abstract 864</b> P.G. Richardson	patients with myeloma refractory to lenalidomide and bortezomib phase I: MTD phase II: open label, Arm A= pomalidomide 4 mg plus low dexamethasone vs. Arm B= pomalidomide 4 mg alone, endpoint is PFS; N=221	pomalidomide 21 of 28 days with and without low-dose dexamethasone; phase I: 2 mg (n=6), 3 mg (n=8), 4 mg (n=14), 5 mg (n=10), total enrollment, N=38; if PD or no response after 4 cycles option to add low dexamethasone at 40 mg per week	grade 3 to 4 myelosuppression was the dominant AE with low incidences of venous thromboembolism (VTE) and PN; =4 mg	phase I: PR or greater 27% for the 4 mg dose, 29% for the 5 mg dose, and 25% overall median OS=79.6 weeks phase II (first 120 efficacy evaluable patients enrolled): best response of at least PR combining both arms by EBMT criteria = 25% and by IMWG criteria = 28%
<b>Abstract 859</b> X. LeLeu	patients with myeloma refractory to at least 2 cycles of lenalidomide and bortezomib and a creatinine clearance (CrCl) of 50 mL/min randomized phase II median follow-up 6.5 for Arm A vs. 7 months for Arm B	Arm A= 4 mg pomalidomide and low dexamethasone for 21 days of 28 per cycle; N=43 Arm B, 28 days of continuous 4 mg pomalidomide plus low dexamethasone; N=41 aspirin or LMWH recommended for all patients	most hematologic AE were neutropenia; some PN, and no DVT; dose reduction for pomalidomide was required for 49% in Arm A vs. 41% in Arm B	ORR 42% for Arm A vs. 39% for Arm B TTR was 2 months for Arm A vs. 1.7 months for Arm B PR = 33% for Arm A, 34% for Arm B time to progression (TTP) similar in both arms; 5 vs. 6 deaths, 88% vs. 85% of patients surviving at 6 months

## Elotuzumab, a monoclonal antibody (mAb)

**Elotuzumab In Combination with Lenalidomide and Dexamethasone In Patients with Relapsed Multiple Myeloma: Interim Results of a Phase II Study (Abstract 986)** was presented by Paul G. Richardson, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA.

Elotuzumab (HuLuc63) is a humanized monoclonal antibody (mAb) targeting CS1, a cell surface glycoprotein highly and uniformly expressed on myeloma cells, with restricted expression on natural killer (NK) cells. In phase I studies of 5, 10, and 20 mg/kg, elotuzumab-related AEs were primarily infusion-related in 89% patients, mostly grade 1 to 2, with no DLT, and MTD was not reached. Median time to progression (TTP) was not reached at a median follow-up of 12.7 months. Elotuzumab saturated the CS1 binding sites in bone marrow myeloma cells at 10 mg/kg.

**Objectives of phase II:** to evaluate the ORR of the elotuzumab plus lenalidomide and dexamethasone in patients with relapsed/refractory myeloma after 1 to 3 prior therapies, and to evaluate doses of 10 and 20 mg/kg.

**Doses:** elotuzumab weekly for the first 4 cycles, then every other week; lenalidomide 25 mg; low-dose dexamethasone weekly; Solu-Medrol (methylprednisolone) at the equivalent of 10 mg of dexamethasone and other drugs to prevent infusion reactions.

**Patients:** no prior lenalidomide, most had a prior transplant, most had received prior thalidomide; safety population N= 63 receiving 10 mg/kg doses (n=31) or 20 mg/kg doses (n=32).

**Side effects:** The AE profile was mostly as expected with lenalidomide and dexamethasone. Higher-grade hematologic AE were as expected and were manageable. Elotuzumab-related AE included fatigue and low-grade fever and were manageable. There was no treatment-related mortality. Infusion reactions occurred in 89% in the phase I portion of this trial, but with phase II management this was cut in half. Infusion reactions were typical of those associated with mAbs.

**Results:** ORR was 90% with the 10 mg/kg dose. The best confirmed response of at least PR occurred in 90% of patients on the 10 mg/kg dose and in 72% of patients on the 20 mg/kg dose. The study was not powered to determine the differences between doses; both doses had a sCR/CR rate of 5%. At least VGPR occurred in 37% of patients overall, and was 42% for the 10 mg/kg dose. Patients with higher beta-2-microglobulin (B2M) responded. Median time to best response was 2 months for both arms. Median follow-up was 4.9 months, and median PFS was not reached, which Dr. Richardson called encouraging. At both doses CS1 was saturated on CD38+ and CD138+ cells. The 10 mg/kg dose is recommended for the open label phase III trial to start next year.

## **New Targeted Therapies in Early Trials**

Early trial results for two new targeted therapies in early clinical trials are summarized in Table 3. The PI3K (phosphoinositol 3 kinase) pathway is important in enhancing cell survival by stimulating cell proliferation and inhibiting apoptosis. mTor (mammalian target of rapamycin) inhibitors may overcome resistance to bortezomib because they are synergistic with bortezomib in vitro and in co-culture. PD0332991 is a selective, reversible, orally bioavailable inhibitor of cyclin-dependent kinases (CDK) 4 and 6. CDK4/6 are two positive regulatory factors involved in the cell cycle that are associated with phosphorylation of Rb and increasing cell proliferation with disease progression in myeloma. PD0332991 has a low toxicity and there is a reproducible functional assay for patient samples. PD0332991 is thought to have high specificity for CDK4/6. Induction of prolonged G1 arrest by inhibition of CDK4/6 may disrupt coupling of gene expression from the cell cycle, thereby sensitizing cells to killing by other agents, e.g. lenalidomide or bortezomib. Because this inhibition is reversible, release from G1 arrest may synchronize cells and improve killing by bortezomib. Note that temsirolimus, an mTOR inhibitor, is approved for advanced renal cell carcinoma, whereas PD0332991 is still investigational.

### **mTOR (Mammalian Target of Rapamycin)**

#### **Final Results of the Phase I/II Trial of Weekly Bortezomib In Combination with Temsirolimus (CCI-779) In Relapsed or Relapsed/Refractory Multiple Myeloma**

**Specifically In Patients Refractory to Bortezomib (Abstract 990)** was presented by Irene M. Ghobrial, Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA.

**CDK4/CDK6 (Cell Cycle)**

**A Phase I Study of PD 0332991: Complete CDK4/6 Inhibition and Tumor Response In Sequential Combination with Bortezomib and Dexamethasone for Relapsed and Refractory Multiple Myeloma, (Abstract 860)** was presented by Ruben Niesvizky, MD, Medicine and Hematology/Oncology, Weill Cornell Medical College, New York, NY.

**Table 3. Summary of New Targeted Therapy Trials**

<b>Abstract First Author</b>	<b>Patients Phase Follow-up</b>	<b>Agents and Doses</b>	<b>Side Effects</b>	<b>Responses</b>
<b>Abstract 990</b> I.M. Ghobrial	patients had $\geq 1$ prior therapy and were heavily pretreated with dexamethasone; most had received thalidomide, bortezomib, and lenalidomide phase I (dose-escalation) n=20 Phase II n=43	IV temsirolimus at 15 to 25 mg weekly on days 1, 8, 15, 22, and 29 of 35 day cycles bortezomib at 1.3 to 1.6 mg/m <sup>2</sup> weekly on days 1, 8, 15, and 22 dexamethasone not permitted	phase I: the most common AE was thrombocytopenia; 1 death due to septic shock phase II: toxicities included thrombocytopenia and fatigue; no sensory neuropathy due to temsirolimus or weekly bortezomib; 3 deaths	phase II: ORR=40% excluding 3 unevaluable patients; in with bortezomib-resistant disease ORR=20%; in bortezomib-sensitive disease ORR=53% median PFS=5 months median TTP=5.7 months
<b>Abstract 860</b> R. Niesvizky	patients with symptomatic relapsed and/or refractory myeloma after >1 treatment who were Rb positive and had disease with a high proliferation rate phase I dose escalation study; determine MTD for Phase II	PD0332991 in combination with bortezomib and dexamethasone, given on two different schedules Schema A: PD0332991 daily for 21 days plus bortezomib and dexamethasone, n=9 schema B: PD0332991 daily for 11 days plus bortezomib and dexamethasone, n=12: used for phase II: PD0332991 will be 100 mg, bortezomib 1.0 mg/m <sup>2</sup> and dexamethasone 20 mg	schema A: DLTs required dose reductions; Schema B: DLT at the first dose escalation AEs were related to the combination of PD0332991 and bortezomib and included cytopenias	PD0332991 abrogated phosphorylation of Rb in 80% of patients; 1 patient on each Schema had VGPR

## Maintenance Therapy

**IMF Symposium: Case Study 4: Consolidation and Maintenance Therapy in Myeloma** was presented by Phillippe Moreau, MD, University Hospital Hôtel-Dieu, Nantes, France.

Dr. Moreau discussed whether patients with VGPR after autologous stem cell transplant (ASCT) need additional treatment, and if so, what kind. In 2009, the IMWG updated its definition of stringent CR to require negative clonal cells by multiparametric flow cytometry (minimum of 4 colors). Stringent CR (sCR) is defined as CR plus the absence of phenotypically aberrant plasma cells in the bone marrow with a minimum of 3000 total plasma cells analyzed by multiparametric flow cytometry (“immunophenotypic CR”). Molecular CR was also incorporated into the IMWG (the IMF-sponsored International Myeloma Working Group) criteria and is defined as stringent CR plus negative ASO-PCR (allele-specific oligonucleotide polymerase chain reaction). Because depth of response and time to progression are correlated, it is important to identify the best consolidation therapy after ASCT. The BMT-CTN phase III study will randomly assign patients to no consolidation vs. consolidation with VRD x 4 or with Mel (melphalan); all patients receive Mel 200 so the Mel consolidation is a second ASCT. All groups will then receive lenalidomide maintenance. The new IMWG criteria will be used to assess response.

Dr. Moreau reviewed published and on-going studies of maintenance therapy. IFM 2005-02 supports lenalidomide maintenance after ASCT, showing improved PFS but no OS advantage. The CALGB 100104 study is an ongoing phase III trial of lenalidomide vs. placebo as maintenance after ASCT. PFS and TTP are improved in the lenalidomide arm but there is no difference in OS (see below). The HOVON-65/GMMG-HD4 is another ongoing phase III trial. An additional trial, MM-015, is comparing melphalan plus prednisone plus lenalidomide followed by lenalidomide maintenance (MPR-R) vs. MPR vs. MP for long-term control in newly diagnosed myeloma. PFS at the first interim analysis showed a 50% reduction risk. MPR-R vs. MPR in a landmark analysis of PFS after cycle 9 showed a 75% reduced risk. Again, there is no difference in OS. The FIRST study of lenalidomide and low-dose dexamethasone vs. MP (MP plus thalidomide) (IFM 07-01) included almost 1600 patients and just closed to enrollment. Lenalidomide and low-dose dexamethasone until progression is being tested in one arm. During the discussion, it was noted that lenalidomide maintenance outside of the clinical trial setting is allowed in the US but not in Italy, France, or Spain. Data supporting bortezomib maintenance therapy have also been presented. How long to give maintenance therapy is not known.

The results of three maintenance studies are summarized in Table 4.

**Thalidomide Maintenance Significantly Improves Progression-Free Survival (PFS) and Overall Survival (OS) of Myeloma Patients When Effective Relapse Treatments Are Used: MRC Myeloma IX Results (Abstract 623)** was presented by Gareth J Morgan, Institute of Cancer Research, The Royal Marsden Hospital, London, United Kingdom.

**Maintenance Treatment with Lenalidomide After Transplantation for Myeloma: Final Analysis of the IFM 2005-02 (Abstract 310)** was presented by Michel Attal, MD, Hôpital Purpan, Toulouse, France.

**Phase III Intergroup Study of Lenalidomide Versus Placebo Maintenance Therapy Following Single Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Multiple Myeloma: CALGB 100104 (Abstract 37)** was presented by Philip L. McCarthy, MD, BMT Program, Roswell Park Cancer Institute, Buffalo, NY.

**Table 4. Summary of Maintenance Studies**

<b>Abstract First Author</b>	<b>Patients Phase Follow-up</b>	<b>Agents and Doses</b>	<b>Side Effects</b>	<b>Responses</b>
<b>Abstract 623</b> G. Morgan	820 patients	thalidomide or no maintenance (half to each arm) median 7 months of maintenance	high rate of PN led to slightly over half of patients discontinuing maintenance	PFS significantly longer for patients on thalidomide maintenance overall with most benefit for those with favorable FISH; no difference in OS
<b>Abstract 310</b> M. Attal	614 patients under age 65 years with non-progressive disease within 6 months of ASCT; phase III median F/U 34 months post-random assignment	placebo (n=307) or lenalidomide (n=307) maintenance therapy	discontinuation rate 15% for placebo vs. 21% with lenalidomide; lenalidomide caused significant non-febrile neutropenia, and 2% DVT vs. 0 for placebo recommendation to monitor for second malignancies	CR and PFS improved with lenalidomide maintenance 4 factors associated with improved PFS: lenalidomide maintenance, VGPR after consolidation (most important), no del 13, and low $\beta$ 2M no differences in OS 5 years post-diagnosis between groups (80%).
<b>Abstract 37</b> P. McCarthy	patients with stable disease (SD) or better within a year of induction therapy and ASCT Mel 200	placebo (n=229) or lenalidomide maintenance (n=231) at a starting dose of 10 mg/day, escalated to 15 mg/day after 3 months, and continued until PD, with dose reductions or discontinuation if necessary for toxicity	lenalidomide maintenance associated with significantly more AE, including thrombocytopenia, neutropenia, febrile neutropenia, and infections 15 new malignancies after randomization in patients receiving lenalidomide vs. 6 in the placebo arm	lenalidomide associated with 60% reduction in the risk of disease progression or death vs. placebo median TTP for lenalidomide = 42.3 months vs. 21.8 months for placebo TTP independent of $\beta$ 2M levels or prior lenalidomide or thalidomide OS not yet published

## Myeloma Biology

### Bisphosphonates and Bone Disease

There were two presentations on sub-analyses of the MRC Myeloma IX trial concerning myeloma bone disease.

**Optimising Bone Disease In Myeloma; Zoledronic Acid Plus Thalidomide Combinations Improves Survival and Bone Endpoints: Results of the MRC Myeloma IX Trial (Abstract 311)** was presented by Gareth J Morgan, Section of Haemato-Oncology, The Institute of Cancer Research, London, United Kingdom.

**Objectives:** This presentation focused on randomization to zoledronic acid or clodronate in both treatment arms (intense and non-intense) in the MRC Myeloma IX trial. Note that zoledronic acid is available in the US, but clodronate is not (although it is available in Canada, the UK, and other countries).

**Patients:** Approximately 1960 patients were enrolled in this study; median follow-up is 3.7 years.

**Side effects:** There was no excess renal toxicity. Osteonecrosis of the jaw (ONJ) was significantly higher with zoledronic acid, about 4%, but all incidents were minor and resolved without surgery and with conservative management.

**Results:** Zoledronic acid was associated with significantly improved OS (5.5 month increase) vs. clodronate, and PFS was also increased. Adjustment for skeletal-related events (SRE; defined as pathologic fractures, need for radiation to the bone, bone surgery, spinal cord compression, and similar events) still favors zoledronic acid, suggesting an anti-myeloma effect. Zoledronic acid was associated with higher OS and longer PFS for both intensive and non-intensive treatment groups, although the difference was not significant for the intensive pathway. Zoledronic acid significantly reduced SRE for patients with bone lesions at presentation and for those with no lesions at baseline, suggesting that all patients should be treated even if they have no bone lesions at baseline. Zoledronic acid decreased SRE compared with clodronate during maintenance therapy, and was better than clodronate regardless of induction regimen. Patients receiving thalidomide-containing regimens plus zoledronic acid had the best responses.

**Defining Myeloma Patients at High Risk of Developing Bone Disease While on Bisphosphonate Treatment (Abstract 782)** was presented by Ping Wu, Section of Haemato-Oncology, The Institute of Cancer Research, London, United Kingdom.

**Objectives:** This analysis investigated the molecular basis of bone disease at presentation, and developed a gene expression-based predictor applicable to patients with myeloma at presentation for high risk of developing myeloma bone disease.

**Methods:** Gene expression profiling (GEP) was performed on samples from 261 patients comprising a training set (n=205) and test set (n=56). Differential expression of genes was scored by SAM (significance analysis of microarray).

**Results:** There was a shorter OS in patients presenting with bone disease defined by presence of any lytic lesion or x-ray indication. There were 50 genes associated with bone disease at presentation by SAM score. Of those that were up-regulated, most were involved with growth factors, apoptosis, and transcription factor regulation. This suggests that patients with bone disease have a different myeloma metabolism. The top 10 genes most significantly associated with bone disease at presentation included DKK1 (Wnt signaling inhibitor), RNASEH2B (involved in DNA replication), genes involved in apoptosis, and 2 genes associated with growth factor signaling. FRZB and DKK1 are both up-regulated. In the group of patients with low bone disease, these genes are both down-regulated. Insulin-like growth factor (IGF)-1 is one of the growth factors involved in bone destruction. Two negative regulators of IGF signaling are down-

regulated with bone disease. The time to first SRE (TTFSRE) curve shows rapid onset of events within the first two months for patients treated with zoledronic acid or clodronate in the MRC trial, so they looked at this point of the curve; the SREs level off after this point. There was a 26% relative reduction in all events with zoledronic acid within the first 2 months, which may be related to disease control. Excluding the first 2 months, 97% of patients had their first SREs within 2 months to 2 years. Of the 14 genes identified as associated with SRE development, all are up-regulated in SRE. These include interferon-induced genes reported by UAMS to be associated with poor prognosis.

A 7-gene signature for SRE was developed that has good predictive power. Looking at all patients in the trial, other SRE-associated parameters included t(4;14), hyperdiploidy, presenting bone disease, and high calcium levels. In the gene expression data set high calcium, presenting bone disease, and hyperdiploidy were significantly associated with SRE development; when added individually to the 7-gene signature, only calcium was statistically significant. The sensitivity and specificity of the training set were 87% and 72% respectively; these were validated in the test set. The SRE predictor, which includes the 7 genes plus calcium, is clinically applicable to estimating the risk of SRE before relapse despite a patient being on bisphosphonate treatment. This was validated in subgroups of patients with and without baseline bone disease treated with and without zoledronic acid or clodronate. The genes identified give insight into the biology of underlying SRE development. This test could be used in future clinical trials to identify patients at high risk for bone disease even while on bisphosphonates.

## Renal Impairment

Meletios A. Dimopoulos, Greek Myeloma Study Group, Greece, presented **Renal Insufficiency and Failure as part of the Multiple Myeloma Education Program: Supportive Care in Plasma Cell Dyscrasias**, chaired by Pieter Sonneveld, MD, PhD, Erasmus University Medical Center, Rotterdam, Netherlands.

The main points include the following:

- Renal function should be assessed in patients with myeloma. Diagnosis involves evaluation of serum creatinine, urinary Na, K, Ca, calculation of estimated glomerular filtration rate (eGFR) using the MDRD formula, determination of total protein in a 24-hour urine sample, urine protein electrophoresis (UPEP) and immunofixation, and serum free light chains (FLC).
- Management of myeloma-associated renal dysfunction includes hydration, alkalinizing the urine, managing hypercalcemia, treating infections, and avoiding nephrotoxic agents while managing the myeloma. High-dose steroids may be effective. Plasma exchange with hemodialysis or hemodialysis alone does not appear to be very effective, although high cut-off permeability filters could remove large amounts of FLC.
- Doses of melphalan should be reduced with renal impairment.
- Thalidomide has negligible renal excretion, so it can be used in patients with renal dysfunction, but there are case reports of associated hypokalemia. Thalidomide may reverse renal impairment in some patients.
- Because lenalidomide is primarily excreted by the kidneys, dose reduction, based on creatinine clearance (CrCl) is mandatory in renal impairment.

- There is a strong rationale for using bortezomib in patients with renal impairment. Pharmacokinetics are independent of renal function, there is a rapid response, and bortezomib is generally well tolerated; about 50 to 60 % of patients experience improved renal function. Dialysis may be avoided or no longer required in some patients treated with bortezomib. Improved renal function has also been seen in bortezomib-based combination therapy. Bortezomib should be given after dialysis.
- IMWG proposes bortezomib-based therapy in patients with renal impairment with high-dose dexamethasone, possibly with the addition of a third agent, e.g., thalidomide, cyclophosphamide, or doxorubicin, and is recommended for patients with renal impairment of any grade.

## Targeting the Myeloma Stem Cell

### **Ad Hoc Scientific Committee on Plasma Cell Biology: Targeting the Myeloma Stem Cell.**

Chair Raymond Powles, Parkside Oncology Clinic, Wimbledon, United Kingdom, said that the committee will change its name to Plasma Cell Neoplasia.

William Matsui, MD, Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD, presented **The Origin of the Myeloma Stem Cell (SCI-4)**, and discussed the concept of myeloma cancer stem cells. His main points include the following:

- Clonogenic tumor cells are rare. Relapse in cancer requires chemoresistance and clonogenic potential. It is possible that chemotherapy removes tumor cells but cancer stem cells have intrinsic drug resistance. It is not clear if tumorigenic cells in myeloma are involved in initiation, relapse, or progression.
- Patient-specific factors, including disease stage and type (MGUS, myeloma, PCL), whether newly diagnosed or relapsed, as well as genetics, e.g., presence of hyperdiploidy vs. Ig-translocations, affect the ability to isolate putative myeloma stem cells.
- To identify potential targets of small molecules that might be used to attack myeloma stem cells, a discovery approach using GEP and proteomics is required. For this, a homogenous cell population is needed and it has not been possible to achieve this yet in any cancer.
- Treatment of myeloma requires targeting two compartments: plasma cells and stem cells. It has been reported that Rituximab could target stem cells; if it did so in myeloma, then cyclophosphamide could be used to debulk plasma cells, followed by more Rituximab for residual stem cells.
- There is a need for novel clinical trial designs to detect activity against the small population of tumor cells. Stem cell-based biomarker strategies need to be developed.

Martin Pérez Andrés, PhD, Universidad de Salamanca, Salamanca, Spain, discussed **Immunophenotypic Analysis of Myeloma Precursors: Antigens for Therapeutic Targeting (SCI-5)**. He proposed three features that all tumor stem cells should have: ability to differentiate, ability to self-renew, and resistance to therapy. He reviewed properties of putative myeloma precursor cells, reiterating that the clonogenic fraction is small. The strongest evidence for them is the ability to reproduce tumors in vitro and in vivo. He believes these cells have features of

germinal center cells, that is, B cells not plasma cells, although not everyone agrees. His hypothesis is that a precursor cell in the plasma cell compartment needs to circulate to spread throughout bone marrow. Another hypothesis is that the cells derive from memory B cells. Whatever model is correct, it should be possible to find myeloma precursor cells in the peripheral blood, in part because in aggressive and end-stage disease, extramedullary disease occurs as a result of spread via the circulation. There is some evidence that important tumorigenic activity is occurring within the plasma cell compartment.

Constantine S. Mitsiades, MD, PhD, Jerome Lipper Multiple Myeloma Disease Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, presented **How to Overcome Myeloma Stem Cell Resistance to Therapy - Targeting the Stem Cell Niche (SCI-6)**. The main points of this presentation include the following:

- Mechanisms of drug resistance in myeloma include differential dependence on oncogenic pathways compared with the bulk of the tumor population, e.g., hedgehog, notch, and Wnt signaling pathways. These pathways all have multiple ligands and receptor proteins, are complex, and interact with each other, providing multiple points in these pathways that can be targeted in myeloma and other cancers. Agents targeting these pathways are in clinical development. Although mutations activating these pathways seem to occur in other cancers, they have not been seen in myeloma.
- A caveat to targeting developmental pathways in cancer stem-like cells is that agents developed to do so may have side effects on normal stem cells.
- There is an additional need to screen agents against the myeloma stem cells in the presence of accessory (stromal) cells. Some developmental pathways or cancer stem cell pathways seem to be more active in the presence of bone marrow stromal cells (BMSC), maybe because they target the interactions or have multi-target effects. Any agent targeting “stemness” needs to be tested in the presence of the local microenvironment.
- It is not known if most of the tumor is capable of reverting back to stem cell-like cells, and if there is bi-directional transition of tumor cells between stem cell-like and non-stem cell-like states, likewise between drug resistant and non-resistant states, and if these are influenced by the microenvironment.

## Side Effects of Therapy

### Neuropathy

Pieter Sonneveld, MD, PhD, Department of Hematology, Erasmus University Medical Center, Rotterdam, Netherlands, presented **Dealing with Neuropathy** as part of the **Multiple Myeloma Education Program: Supportive Care in Plasma Cell Dyscrasias**, which he chaired. The talk is summarized here. Important points include the following:

- In all plasma cell diseases, up to 54% of newly diagnosed patients, including those with MGUS, myeloma, POEMS, and Castleman disease, have peripheral neuropathy (PN). PN is also associated with amyloidosis and cryoglobulinemia.
- The causes of baseline PN in myeloma include mechanical compression of nerves, including the spinal cord; radiculopathy; carpal tunnel syndrome; hyperviscosity; diabetes; vitamin

deficiencies, e.g., of B12; and possibly genetic susceptibility.

- Treatment with vincristine and cisplatin, which are not used much any more in myeloma, thalidomide, and to a lesser extent lenalidomide and pomalidomide, and the proteasome inhibitors bortezomib and carfilzomib, are associated with PN. PN is one of the most frequent non-hematologic side effects of myeloma therapy and has a serious impact on patient QoL, including physical, social, and psychological functions. It is also frustrating for the physician, and may interfere with patients continuing therapy.
- The anatomic damage caused by thalidomide and bortezomib are different. Axons are damaged more by thalidomide, whereas bortezomib is toxic to small afferent fibers. Carfilzomib causes less sensory PN (less than 15%) than bortezomib.
- Thalidomide causes mixed sensory motor PN with degeneration of the longest axons, inhibits vascular supply to nerves, and leads to demyelination, which may be irreversible. Thalidomide-emergent PN can be predominantly sensory or sensorimotor, with symmetric hypoesthesia, tingling, or hyperesthesia of the fingers and toes. Motor PN occurs less frequently than sensory PN. Symptoms such as cramps, weakness, or tremor must be differentiated from steroid-induced effects in patients taking thalidomide with steroids.
- Bortezomib-emergent PN is typically sensory, and presents as hyperesthesia, hypoesthesia, tingling, or temperature sensitivity, and causes burning sensations in the soles and palms, starting distally with possible progression to proximal PN. Bortezomib-associated motor PN, if present, follows sensory PN. Autonomic PN may present as orthostatic hypotension, sexual dysfunction, or constipation, and generally appears and progresses slowly. Lower bortezomib doses are associated with a lower incidence of PN.
- Both thalidomide and bortezomib-associated PN are time dependent and dose dependent. PN associated with thalidomide is minimally reversible, and takes years to resolve. Bortezomib-associated PN improves or resolves in 2 to 3 months in 70% of patients. To manage PN, doses of bortezomib or thalidomide should be modified.
- The key to intervention is prevention, because there is little treatment, and prevention is more important than medication. Vitamin C may interfere with bortezomib efficacy. Tricyclic antidepressants, anti-seizure medications, selective serotonin norepinephrine reuptake inhibitors (SSNRIs), calcium channel blockers, and other agents have been used to treat PN. Supplements, vitamins, and minerals are sometimes recommended, but have not been tested in clinical trials.

**Two studies assessing peripheral neuropathy are summarized in Table 5.**

**Development of Bortezomib-Induced Peripheral Neuropathy (BiPN) In Multiple Myeloma: Incidence and Molecular Characterization In Newly Diagnosed Patients Treated with Bortezomib (Abstract 304)** was presented by Annemiek Broyl, MD, Hematology, Erasmus MC, Rotterdam, Netherlands.

**A Phase III Prospective Randomized International Study (MMY-3021) Comparing Subcutaneous and Intravenous Administration of Bortezomib In Patients with Relapsed Multiple Myeloma (Abstract 312)** was presented by Philippe Moreau, University Hospital, Nantes, France.

**Table 5. Summary of Peripheral Neuropathy Studies**

Abstract First Author	Patients Phase Follow-up	Agents and Doses	Side Effects	Results
<b>Abstract 304</b> A. Broyl	patients with myeloma (n=369) phase III prospective, randomized trial (HOVON65/GMMG-HD4) sub-study to analyze genetic variation associated with BiPN the “Bank on a Cure” (BOAC) SNP chip, containing 3404 SNPs in functional regions within 983 cellular function genes and pathways	induction therapy with bortezomib (PAD; n=250) followed by bortezomib maintenance vs. conventional vincristine (VAD; n=250) induction therapy followed by thalidomide maintenance	incidence of early onset bortezomib-induced PN (BiPN) (within one treatment cycle) in the bortezomib-treated patients was not significantly different from the incidence of early onset vincristine induced PN (ViPN) in VAD-treated patients late onset (after cycle 2 to 3); BiPN was significantly greater (grade 2 to 4) than ViPN, 25% vs. 7%	Early onset BiPN was associated with genes involved in drug-induced apoptosis, peripheral nervous system development and function, DNA repair, mitochondrial dysfunction, and AMPK signaling. Late-onset BiPN was associated with different genes involved in peripheral nervous system development and function, apoptosis, calcium ion binding, inflammation, transcription regulation, and DNA repair. ViPN was associated with different genetic factors.
<b>Abstract 312</b> P. Moreau	74 patients in the IV arm, 148 patients in the SC arm  phase III randomized study	subcutaneous (SC) bortezomib (2.5 mg/mL) vs. IV bortezomib (1 mg/mL) at the usual dose and schedule dexamethasone after 4 cycles if response was <PR	grade 3 and 4 AE were reduced, but not statistically significantly with SC; 57% for SC and 70% for IV neutropenia significantly reduced with SC administration; thrombocytopenia and anemia the same for SC and IV PN statistically significantly different: any PN 53% with IV vs. 38% with SC; $\geq$ grade 2 PN 41% with IV vs. 24% with SC; $\geq$ grade 3 PN 16% with IV and 6% with SC. Local site reactions (redness) in 6% of patients; 1% of patients had a severe site reaction	ORR=42% in both arms after 4 cycles $\geq$ VGPR for IV = 16% vs. 17% for SC After 8 cycles 52% ORR and 25% $\geq$ VGPR for both arms median TTR=1.4 months in both arms median TTP=9.4 months for IV and 10.4 months for SC 1 year survival=76% for IV and 73% for SC PK and pharmacodynamics are the same, and differences in C <sub>max</sub> and T <sub>max</sub> might explain the improved safety profile with the SC route

## Thrombosis

Sigurdur Y. Kristinsson, MD, PhD, Department of Medicine, Division of Hematology, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, presented **Thrombotic Issues in Myeloma** as part of the **Multiple Myeloma Education Program: Supportive Care in Plasma Cell Dyscrasias**, chaired by Pieter Sonneveld, MD, PhD, Erasmus University Medical Center, Rotterdam, Netherlands. The main points were:

- Patients with cancer, including myeloma, have an increased risk for both venous and arterial thrombosis.
- Thalidomide and lenalidomide increase the risk of venous thromboembolism (VTE). Thalidomide is associated with an increased risk in combination chemotherapy, particularly in newly diagnosed patients; lenalidomide increases the risk in combination with dexamethasone or chemotherapy in either newly diagnosed or relapsed, refractory myeloma.
- Arterial thrombosis occurs in younger patients with myeloma treated with VAD, TAD, or PAD.
- Bortezomib does not cause an increase risk of VTE alone or in combination with dexamethasone or chemotherapy in newly diagnosed or relapsed, refractory myeloma. There have been suggestions that bortezomib has a protective effect in combination with lenalidomide or thalidomide but patients in many studies have been given anti-thrombotic prophylaxis.
- Thrombotic events associated with ASCT may be related to the use of central venous catheters.
- Published guidelines from the IMWG suggest aspirin for patients with no risk factors and LMWH or full-dose warfarin for those with two or more risk factors. Duration of thromboprophylaxis depends on patient- and treatment-related risk factors. Risk is highest at the beginning of treatment, so prophylaxis for 4 to 6 months at least is suggested. There are no studies of thromboprophylaxis in patients with myeloma and renal failure, but if CrCl is less than 30 mL/min, it is best to dose adjust LMWH or use warfarin.
- Treatment of VTE includes stopping thalidomide or lenalidomide, administering full anticoagulation with LMWH or warfarin, and then restarting anti-myeloma therapy.

## Newly Diagnosed Myeloma

### Transplant-Eligible Patients

**IMF Symposium Case 2: Evolving Treatment Approaches in Transplantation-Eligible Patients** was presented by Jesús F. San Miguel, MD, PhD, Hospital Universitario de Salamanca, Salamanca, Spain.

Controversial issues concerning treatment of young patients with myeloma include the optimal induction treatment, the role of high-dose therapy and ASCT, the value of maintenance therapy, treatment according to risk stratification, and the role, if any, for allogeneic transplant. The main points of this presentation were:

- Induction regimens with bortezomib, thalidomide, or lenalidomide yield better responses and longer PFS than VAD.
- Induction with novel agents and ASCT are complementary, but conditioning regimens can be improved by adding bortezomib to melphalan; busulfan plus melphalan is showing promising results.
- The IFM-DFCI trial should answer the question about early vs. late ASCT. Patients receiving early transplant appear to have a higher 3-year OS than those who continued on primary therapy. With up-front transplant patients are more likely to tolerate intensive and repetitive therapies. ASCT is associated with a long treatment-free interval and good QoL, and although relapsed myeloma after high-dose (HD) Mel is sensitive to novel agents, it isn't known whether relapsed myeloma after novel therapies is sensitive to HD Mel.
- In general, thalidomide, lenalidomide, and bortezomib as maintenance therapy have shown benefits.
- Treatment stratification according to risk factors would offer intensive treatment to patients with high-risk disease, and less intense approaches for patients with lower-risk disease or for those who are in CR. If there is no molecular remission, there is a higher risk of relapse. If cure is the goal, under-treating low-risk patients may not be the best approach because they should be the first group of patients who could be cured. Better tools to evaluate treatment efficacy are needed.
- A particular regimen can't be recommended for high-risk disease based on current data, and trials are needed.
- Rather than using allogeneic transplantation, Dr. San Miguel recommends induction with a novel combination, e.g., VRD with or without cyclophosphamide, ASCT with Mel 200 plus bortezomib; then if the patient has CR, maintenance with lenalidomide; if no CR, then consolidation with VRD, then maintenance.

**Four studies in transplant-eligible, newly diagnosed patients with myeloma are summarized in Table 6.**

**A Phase III PETHEMA/GEM Study of Induction Therapy Prior Autologous Stem Cell Transplantation (ASCT) In Multiple Myeloma: Superiority of VTD (Bortezomib/Thalidomide/Dexamethasone) Over TD and VBMCP/VBAD Plus Bortezomib (Abstract 307)** was presented by Dr. Laura Rosiñol, Hospital Clinic, Barcelona, Spain.

**Frontline Therapy with Bortezomib, Lenalidomide, and Dexamethasone (VRD) Induction Followed by Autologous Stem Cell Transplantation, VRD Consolidation and Lenalidomide Maintenance In Newly Diagnosed Multiple Myeloma Patients: Primary Results of the IFM 2008 Phase II Study (Abstract 624)** was presented by Murielle Roussel, Hématologie Clinique, Hôpital Purpan, Toulouse, France.

**Molecular Remission After Bortezomib-Thalidomide-Dexamethasone Compared with Thalidomide-Dexamethasone as Consolidation Therapy Following Double Autologous Transplantation for Multiple Myeloma: Results of a Qualitative and Quantitative Analysis (Abstract 861)** was presented by Carolina Terragna, Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy.

**Tandem Autologous Hematopoietic Stem Cell Transplants (AuHCT) with or without Maintenance Therapy (auto-auto) Versus Single AuHCT Followed by HLA Matched Sibling Non- Myeloablative Allogeneic HCT (auto-allo) for Patients with Standard-Risk (SR) Multiple Myeloma (MM): Results From the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0102 Trial (Abstract 41)** was presented by Amrita Krishnan, M.D., Hematology and Stem Cell Transplantation, City of Hope, Duarte, CA.

**Table 6. Summary of Studies in Transplant-eligible, Newly Diagnosed Patients**

<b>Abstract First Author</b>	<b>Patients Phase Follow-up</b>	<b>Agents and Doses</b>	<b>Side Effects</b>	<b>Results</b>
<b>Abstract 307</b> L. Rosinol	390 patients (130 per arm) GEM05 MENOS65 median F/U = 27 months	n=129 for QT +V (conventional chemotherapy: VBMCP/VBAD plus bortezomib), n=127 for TD, n=130 for VTD	grade 3 to 4 adverse events were similar among the arms; neutropenia was higher for QT+V PN was higher with VTD	CR was significantly higher with VTD (35%) than QTD (21%) or TD (14%); post-ASCT CR was 38% for QT+V, 24% for TD, and 48% for VTD; CR for patients with t(4;14) was higher with VTD; CR for patients with t(11;14) was better with QT+V; OS at 4 years was 76% with no significant differences across groups but was shorter for high-risk patients regardless of treatment
<b>Abstract 624</b> M. Roussel	newly diagnosed younger patients (n=31) phase II open label (IFM 2008)	VRD induction, SC collection, ASCT with HD Mel, consolidation with VRD, maintenance for 12 months with lenalidomide at a dose of 10 mg for 3	almost all patients experienced hematologic toxicities; grade 3 to 4 events included 39% neutropenia (decreased to 26% with dose reduction), 13%	RR improved with each stage of treatment; ≥VGPR was over 80%; CR in almost half of patients

		months; if tolerated, the dose was increased to 15 mg per day continuous	thrombocytopenia, and 6% anemia; PN in 68% of patients, 55% during induction, 13% during consolidation, all grade 1 and 2, requiring bortezomib dose reduction in 23%; 2 TE; 5 needed second-line mobilizing agent for SC collection; collection not possible in one patient	
<b>Abstract 861</b> C. Terragna	young, newly diagnosed patients sub-study of GIMEMA looking for minimal residual disease (MRD) in bone marrow at consolidation using patient-specific IgH gene rearrangements and patient-specific PCR (two primers designed for each)	VTD vs. TD for induction prior to ASCT random assignment to consolidation with VTD (n=34) or TD (32) after ASCT; maintenance for both arms	<b>Results</b>	
			<p>TD arm: 10 of 32 (31%) PCR negative at baseline; at consolidation 15 of 31 (48%) were PCR negative; at F/U, MCR was 37.5%; 41% had persistently positive PCR. VTD arm: 13 of 33 (39%) PCR negative at baseline; at consolidation 21 of 32 (64%) were PCR negative; MCR was 45.5%, and 21 % of patients were persistently PCR positive.</p> <p>An upgrade in PCR-negative status after consolidation occurred with VTD but not TD. PFS was significantly longer for patients who were PCR negative at consolidation</p>	
<b>Abstract 41</b> A. Krishnan	patients biologically assigned to ASCT (n=436) or to alloSCT (n=189) on the basis of availability of an eligible, HLA-matched sibling donor after ASCT phase III	initial ASCT with HD Mel 200 then ASCT or alloSCT on basis of donor graft-versus-host disease (GvHD); prophylaxis was cyclosporine and mycophenolate mofetil. If tandem ASCT, random assignment to maintenance with thalidomide plus dexamethasone (n=217) or observation (n=219) for one year	treatment-related mortality (TRM) at 3 years was significantly higher in the ASCT-alloSCT group (12%) than in the tandem ASCT group (4%)	84% of patients assigned to thalidomide maintenance did not complete it. PFS and OS were similar and results were pooled for all tandem ASCT patients; after the first ASCT, 3-year PFS was similar between groups (46% for tandem ASCT vs. 43% for ASCT-alloSCT), and 3-year OS was 80% vs. 77%. No significant difference in 3-year

				progression/relapse between the tandem ASCT (46%) and ASCT-alloSCT (40%) groups
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## Transplant-Ineligible Patients

**IMF Symposium Case Study 3: Emerging Therapies for Transplantation-Ineligible Patients** was presented by Antonio Palumbo, MD, University of Torino and Italian Multiple Myeloma Study Group, Torino, Italy. The main points were:

- For patients who are not eligible for ASCT, use combinations up front, especially novel agent combinations, because the disease is more likely to be sensitive and there is a higher chance of longer survival.
- PFS is longer with molecular response, e.g., PCR negative. All CR are not the same. Combination therapy may increase the CR rate via profound cytoreduction, whereas continuous therapy prolongs PFS. CR predicts the long-term outcome in elderly patients.
- Toxicity of maintenance therapy with lenalidomide or bortezomib in elderly patients might reduce survival.
- The standard of care for elderly patients should be addition of a novel agent to MP, e.g., MPT (increases PFS and OS, but requires prophylaxis for VTE) or VMP (once-weekly bortezomib as part of VMP does not decrease PFS or OS, and is associated with lower rates of PN and discontinuation). VMPT-VT and MPR are other options, but not for patients over age 75 years because increased dose intensity means increased toxicity and discontinuation. Those age 75 years and above should receive reduced-dose chemotherapy. Further dose reductions may be necessary based on AE.

**Five studies in transplant-ineligible patients with myeloma are summarized in Table 7.**

**Lenalidomide Plus Low-Dose Dexamethasone (Ld): Superior One- and Two-Year Survival Regardless of Age Compared to Lenalidomide Plus High-Dose Dexamethasone (LD) (Abstract 308)** was presented by Dr. David H. Vesole, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ.

**Phase 3b UPFRONT Study: Safety and Efficacy of Weekly Bortezomib Maintenance Therapy After Bortezomib-Based Induction Regimens In Elderly, Newly Diagnosed Multiple Myeloma Patients (Abstract 619)** was presented by Ruben Niesvizky, Center of Excellence for Lymphoma and Myeloma, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY.

**Bortezomib, Melphalan, Prednisone and Thalidomide Followed by Maintenance with**

**Bortezomib and Thalidomide (VMPT-VT) for Initial Treatment of Elderly Multiple Myeloma Patients: Updated Follow-up and Impact of Prognostic Factors (Abstract 620)**

was presented by Antonio Palumbo, Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy.

**Novel Three- and Four-Drug Combination Regimens of Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide for Previously Untreated Multiple Myeloma: Results From the Multi-Center, Randomized, Phase II EVOLUTION Study (Abstract 621)**

was presented by Shaji Kumar, MD, Division of Hematology, Mayo Clinic, Rochester, MN.

**A Phase III Study Evaluating the Efficacy and Safety of Lenalidomide Combined with Melphalan and Prednisone In Patients  $\geq$  65 Years with Newly Diagnosed Multiple Myeloma (NDMM): Continuous Use of Lenalidomide Vs Fixed-Duration Regimens (Abstract 622)**

was presented by Antonio Palumbo, MD, University of Torino, Torino, Italy.

**Table 7. Summary of Studies in Transplant-ineligible Patients**

Abstract First Author	Patients Phase Follow-up	Agents and Doses	Side Effects	Responses
<b>Abstract 308</b> D. Vesole	newly diagnosed patients ECOG study E4A03	LD (lenalidomide plus high dose dexamethasone) vs. Ld (lenalidomide plus low dose dexamethasone) survival of patients treated with LD was inferior at the initial analysis so those on LD crossed over to Ld, which is a confounding variable for a long-term study	toxicity was higher in all age groups receiving high- dose dexamethasone	OS for Ld was superior to that of LD at 1 and 2 years OS across all age groups using an age-smoothing technique to correct for age as a continuous variable; by this method, there is no age group for which high-dose dexamethasone is superior LD results in a higher RR in patients under age 65 years but not improved PFS or OS
<b>Abstract 619</b> R. Niesvizky	newly diagnosed elderly patients ineligible for transplant in the context of a community oncology practice (n=502 for ITT population) F/U is ongoing	8 cycles of induction therapy and 6 cycles maintenance VD ("classic" bortezomib and dexamethasone) vs. VTD (bortezomib and dexamethasone on the same classic schedule plus 100 mg thalidomide) vs. VMP (bortezomib on the same schedule,	for the first 100 patients treatment-emergent grade 3 or more AE were high; PN was significant, especially with VTD, which was also associated with the highest rate of AE overall; grade 3 or higher PN was 15%, 26%, and 20% for VD, VTD, or VMP, respectively, and the respective	PFS for the three arms is similar, around 13 to 17 months, but these are early results; global health improved at the time of maintenance, and the best QoL was seen for the VMP group (poster Abstract 3026)

		<p>melphalan and prednisone on the first 4 days of every other cycle)                  maintenance with 1.6 mg/m<sup>2</sup> of bortezomib once weekly for 4 weeks out of every 5</p>	<p>discontinuation rates were 7%, 17%, and 18%; serious AE (SAE) included pneumonia and thrombosis associated with VT; during maintenance there was no increase in toxicities, including PN or SAE</p>	
<p><b>Abstract 620</b>                  A. Palumbo</p>	<p>patients over age 65 years (n=511); median maintenance duration of 18 months</p>	<p>VMP and no maintenance (n=257) vs. VMPT, adding 50 mg continuous thalidomide for 9 courses, with bortezomib twice monthly as maintenance (VMPT-VT; n=254)</p>	<p>VMPT increases neutropenia to 35%, thrombocytopenia and anemia are similar for both treatments; grade 3 to 4 non-hematologic AE were significantly increased; risks of cardiac toxicity and TE and a non-significant increase in infections with VMPT; decrease in any grade PN for VMP from 43% to 21%, and reduction of grade 3 or 4 PN from 4% to 2% with change of twice- to once-weekly infusion of bortezomib; AE during maintenance included PN in 6% of patients; discontinuation for AEs was around 11%</p>	<p>CR = 24% for VMP, and 42% for VMPT (statistically significant difference)                  no difference in OS between groups; 3 year OS approached 80% for VMP and 85% for VMPT-VT                  landmark analysis at the end of 9 cycles showed a 52% reduced risk of progression for VMPT-VT                  clinical benefit from the 4-drug combination is an increasing CR rate with maintenance prolonging response                  median PFS for VMPT-VT was 37 months; VMPT associated with longer PFS in patients younger than age 75 years; for patients older than 75 years, there was no difference in PFS between treatments</p>
<p><b>Abstract 621</b>                  S. Kumar</p>	<p>patients ASCT-eligible or not eligible phase I/II (NCT00507442) phase I dose escalation of cyclophosphamide and determine regimen for phase II                  median F/U 18 to 21 months                  a phase III trial will compare VDR and VDC-</p>	<p>VDCR (standard bortezomib, 40 mg dexamethasone, cyclophosphamide, and lenalidomide) vs. VDR vs. VDC; VDC-mod (extra dose of cyclophosphamide to improve response rate)                  8 cycles of induction and ASCT or 4 cycles of maintenance</p>	<p>toxicities generally similar across arms: nearly all patients had at least 1 grade 3 AE; 2 on-study deaths in the VDCR arm due to renal dysfunction                  about 15% grade 3 to 4 PN                  neutropenia higher with cyclophosphamide-containing regimens; SC collected in nearly half of patients, and failure to collect occurred in newly diagnosed</p>	<p>CR = 5% to 12%, higher in the VDC-mod arm; about half of patients with CR had MRD; about half the patients in each arm had a best confirmed response of VGPR                  1 year estimated PFS = 85%                  estimated OS at 1 and 2 years were 92% and 76%, respectively for VDCR, and 100% for VDC-mod</p>

	mod		patients	
<b>Abstract 622</b> A. Palumbo	transplant ineligible, elderly patients phase III median F/U 25 months	MPR-R then continuous lenalidomide at 10 mg per day as maintenance vs. MPR with no maintenance; vs. MP with no maintenance	hematologic toxicities the major AEs during induction grade 4 TE in 10% of patients non-hematologic grade 3 to 4 AE included 10% infection and 2% to 5 % pulmonary embolism (PE) and DVT AE during maintenance included a low rate of cytopenias due to shorter follow-up and dose reductions to avoid discontinuation; low rate of infection, some late thrombosis discontinuation rate higher for patients over the age of 75 years up to 3% solid tumors occurred (2% with MPR-R), 2% AML, and less than 1% MDS, but the risk of secondary tumors is higher with alkylating agents	$\geq$ VGPR = 30% for MPR and MPR-R, 3 times higher than with MP (60% reduced risk of progression overall, 69% for patients age 65 to 75 years, 61% for patients over age 75 years) PFS = 31 months for MPR-R, 14 months for MPR, and 13 months for MPT MPR-R associated with longer PFS for patients under the age of 75 years, with ISS stages I and II, and with lower $\beta$ 2M 69% reduced risk of progression after 9 cycles of MPR with lenalidomide maintenance, significantly better than MPR without maintenance no difference in OS among treatments; 1-year survival about 92%, 2-year survival 75% to 82%

## Relapsed/Refractory Myeloma

Sagar Lonial, MD, Hematology and Medical Oncology, Emory University, Winship Cancer Institute, Atlanta, GA presented **Relapsed Multiple Myeloma** as part of the **Multiple Myeloma Education Program on Advances in the Basic Science of Plasma Cell Disorders**, which he chaired.

Dr. Lonial discussed new treatments and approaches for the management of relapsed disease. OS and event-free survival (EFS) are poor in patients with disease resistant to bortezomib, thalidomide, and lenalidomide. The options in the relapsed setting include existing novel agents, existing older agents, and new agents in clinical trials. Early relapse should be treated with combination therapy; later relapse with a single agent. If the previous myeloma was aggressive, when it relapses it will require therapy sooner. Transplant-based salvage would be appropriate for patients with DOR after their first transplant of 18 to 24 months. The second duration of remission is usually shorter. It may offer a benefit for patients with pancytopenia that limits further therapy on or off clinical trials. The goal of salvage transplant may be to restore hematopoiesis to allow further chemotherapy treatment. Patients with aggressive, rapid, multiple relapses require combination therapy, and therapy should not be delayed until symptomatic

relapse. Transplant-based therapy is short lived in this setting but offers quick disease control and reconstitution of bone marrow, allowing patients to receive aggressive maintenance therapy after. Ablative allogeneic transplant has a high transplant-related mortality (TRM), up to 40 to 50% within 1 year. Non-myeloablative transplant has a lower risk of TRM but equivalent mortality at 2 years. Graft vs. host disease (GvHD) and relapse are issues beyond 2 years.

Dr. Lonial's talk ended with a summary of some of the new agents in development, including:

- Pomalidomide, an IMiD structurally similar to thalidomide and lenalidomide, but functionally different.
- New proteasome inhibitors: carfilzomib, CEP 18770, NPR-0052
- HDAC inhibitors, which target DNA methylation, including panobinostat, vorinostat, and romidepsin, which may be synergistic with bortezomib. Panobinostat and vorinostat may be synergistic with lenalidomide.
- Agents that target the PI3K/Akt pathway and downstream targets include the Akt inhibitor perifosine, which enhances bortezomib-induced cytotoxicity, and mTOR inhibitors, which are also being tested in combination with bortezomib.
- Monoclonal antibodies, including elotuzumab.

Dr. Lonial concluded that there is no easy algorithm for treating relapsed myeloma. Patient-specific issues, prior therapy, and FISH and cytogenetics should be considered and used to guide treatment decisions.

**Combination of Bendamustine, Lenalidomide, and Dexamethasone In Patients with Refractory or Relapsed Multiple Myeloma Is Safe and Highly Effective: Results of a Phase I Clinical Trial (Abstract 989)** was presented by Suzanne Lentzsch, Department of Medicine, Division of Hematology/Oncology, University of Pittsburgh School of Medicine and Cancer Institute, Pittsburgh, PA

**Objectives:** The objectives of this study included determining MTD, safety, and the dose for a phase II study of bendamustine, lenalidomide, and dexamethasone.

**Doses:** Bendamustine was given on days 1 and 2, lenalidomide on days 1 to 21, dexamethasone on days 1, 8, 15, and 22 at 40 mg in 28-day cycles for a maximum of 8 cycles and 2 beyond the best response. Doses of bendamustine and lenalidomide were escalated with a fixed dose of dexamethasone for three dose levels.

**Patients:** Patients with relapsed or refractory myeloma who were not transplant eligible (N=25) were included.

**Side effects:** There were no DLTs at level 1; at level 2 there was one instance of neutropenia, at level 3 there were several. The MTD was 75 mg bendamustine, 10 mg lenalidomide. There were no grade 4 non-hematologic events; grade 3 events included fatigue. Hematologic events included cytopenias; grade 3 to 4 AE were mostly myelosuppression. Grade 1 PN occurred in 20%, grade 2 in 8%, with no grade 3 or 4 PN. All serious AE resolved (n=3). Patients received aspirin and no TE were seen.

**Results:** The best responses after 2 or more cycles in 23 evaluable patients were ORR 66%, clinical benefit response 91%, at least PR 66%. Median follow-up was 8.8 months. PD occurred in 13 patients, and 4 died. Time to best response was 1.8 months, TTP was 4.3 months, time to next therapy was 6.7 months, and the trial is still ongoing, with the last patient enrolled. Treatment was tolerated in patients up to age 81 years (range 40 to 81 years), and was active in heavily pretreated patients.

## Diagnosis, Risk Stratification, and Staging

### MGUS and SMM

Dr. Ola Landgren, MD, PhD, Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, presented **MGUS and Smoldering Myeloma: New Insights Into Pathophysiology and Epidemiology** as part of the **Multiple Myeloma Education Program on Advances in the Basic Science of Plasma Cell Disorders**, chaired by Sagar Lonial, MD, Emory University School of Medicine, Atlanta, GA.

To answer the question whether myeloma is always preceded by MGUS, the National Institutes of Health (NIH) conducted a prospective screening study for cancers, which identified 71 patients who developed multiple myeloma. In these patients, myeloma was always preceded by MGUS. The FLC ratio was abnormal in many before the development of myeloma. The M-spike significantly increased over time as the time of diagnosis of myeloma approached. Two patterns were identified: half the patients had an evolving M-spike, and half had no M-spike. They are currently looking at whether these populations are different. NIH/National Cancer Institute (NCI) has an ongoing prospective natural history and molecular profiling study. All costs are covered to get patients to the study site. The vast majority of patients with MGUS will never progress to myeloma, so at this time there is no indication for screening for MGUS in the clinic. Patients with SMM should be considered for clinical trials. Outside of clinical trials, observation is still considered the standard of care. Better understanding of the pathogenesis from MGUS to myeloma is needed. Dr. Landgren observed that there are 3 million people with MGUS in the US, and only about 20,000 patients each year are diagnosed with myeloma. They are now screening to identify patients with MGUS who didn't progress to myeloma. Patients with MGUS should be made aware of the symptoms of transformation because they were the most likely to know when transformation or progression is occurring.

### Ultra-High Risk Myeloma

Hervé Avet-Loiseau, MD, PhD, University Hospital of Nantes, Nantes, France presented **Ultra high-risk multiple myeloma** as part of the **Education Program: Understanding and Managing Ultra High-Risk Hematologic Malignancies** chaired by Elihu J. Estey, MD, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA. The main points of this presentation include the following:

- An arbitrary definition of ultra high-risk myeloma is patients having a survival of 24 months regardless of their age. This is in contrast with median survival in the IFM trials for those under age 65 years of almost 8 years and for older patients of somewhat over 4 years.
- Extrinsic factors contributing to high-risk myeloma include  $\beta$ 2M and lactate

dehydrogenase (LDH).

- Intrinsic factors contributing to high-risk myeloma include plasma cell proliferation, leukemic presentation, and certain genetic changes. Important chromosomal abnormalities include t(4;14) and 17p deletion.
- The ISS stage is also prognostic. For patients of any age, survival curves differ depending on stage; those over age 65 years with ISS stage III have a median OS of less than 24 months, for those under age 65 years OS is probably about 28 months.
- Several groups are identifying GEP profiles, SNPs, and chromosomal copy number abnormalities that are associated with good or poor prognosis and that when combined with  $\beta$ 2M could be used to define the population with poor survival.
- Plasma cell leukemia or leukemic presentations have a very poor prognosis but there are no publications with a large number of patients with this condition.
- High-risk myeloma can be defined currently as ISS stage III, presence of del 17p, poor risk genomics by GEP or SNP array, or leukemic presentation.
- Classical induction regimens such as VAD, TD, or bortezomib combinations are not active, and Dr. Avet-Loiseau proposes treating with a rotation of combinations of active drugs, including bortezomib, lenalidomide, dexamethasone, cyclophosphamide, and possible doxorubicin for long-term treatment to reduce the aggressive myeloma clone. HD Mel may be useful for patients under age 65 or 70 years, although the effective number of courses is unknown. Bortezomib could be added; possibly VTD or VRD could be used. Maintenance therapy for patients with high-risk myeloma is also an open question; thalidomide may be deleterious, and little benefit has been shown for bortezomib or lenalidomide.
- There is an urgent need for a universal definition of ultra high-risk multiple myeloma and a need for international trials in this patient group. Additionally, there is a need to identify risk factors in phase III trials of agents such as carfilzomib, pomalidomide, elotuzumab, and HDAC inhibitors, with the goal of identifying drugs for these high-risk patients, who may constitute as much as 20% of the myeloma patient population.

## **Diagnosis, Prognosis, and Risk Assessment**

**IMF Symposium: Case Study 1: Diagnosis, Prognosis, and Risk Assessment in Multiple Myeloma** was presented by S. Vincent Rajkumar, MD, Mayo Clinic, Rochester, MN. Major points of this presentation include the following:

- Positron emission tomography (PET scan) can indicate myeloma disease that is not otherwise apparent, and can determine if the spinal cord is compromised. For SMM and solitary plasmacytomas, magnetic resonance imaging (MRI) of the entire spine can be used to confirm the diagnosis and to determine the extent of disease when symptoms don't agree with the skeletal survey. Lytic bone lesions are seen in 67% of patients at presentation; the use of PET-CT (computed tomography) or MRI can detect more.
- Current IMWG response criteria use FLC if patients lack measurable disease (M-spike). FLC is also used for risk stratification of patients with MGUS, SMM, and solitary plasmacytomas, and for screening in lieu of UPEP because it is easier to do a serum assay

than to collect a 24-hour urine sample.

- A work-up of myeloma should consist of M-protein analysis using serum protein electrophoresis (SPEP; detection rate is 82%) or serum immunofixation electrophoresis (IFE; detection rate is 93%); if FLC or UPEP/UIFE is added, M-protein detection rises to 97-98%.
- The Durie-Salmon staging system has stood the test of time and is still useful to determine tumor burden. For the ISS a diagnosis of myeloma must be confirmed first; then ISS can be used to stage the disease.
- The role of GEP in risk stratification remains to be determined.  $\beta$ 2M is a prognostic factor because it is a surrogate for renal failure and high tumor burden, and a patient presenting with renal failure needs the best available therapy early on.

### Genetic Factors

Three studies assessing the role of genetic factors in myeloma are summarized in Table 8.

**Clinical Outcome According to Both Cytogenetic Abnormalities (CA) Detected by Fluorescence In Situ Hybridization (FISH) and Hyperdiploidy Assessed by Flow Cytometry (FCM) In Elderly Newly Diagnosed Myeloma Patients Treated with A Bortezomib-Based Combination, (Abstract 309)** was presented by María Victoria Mateos, University Hospital of Salamanca, Salamanca, Spain.

**Prognostic Impact of Genetic Subgroups and Development of Gene Classifiers for Response, PFS and OS In Multiple Myeloma Patients Treated with Bortezomib or Conventional Agents In HOVON65/GMMG-HD4 Trial (Abstract 445)** was presented by Annemiek Broyl, MD, Department of Hematology, Erasmus MC, Rotterdam, Netherlands.

**Bortezomib-Based Induction Treatments Improve Outcomes of Newly Diagnosed Multiple Myeloma Patients with High-Risk Cytogenetic Abnormalities (Abstract 781)** was presented by Michele Cavo, Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy.

**Table 8. Summary of Studies in Assessing Genetic Factors**

Abstract First Author	Patients Phase Follow-up Agents and Doses	Genetic Analysis	Results
Abstract 309 M.V. Mateos	patients age greater than 65 years (n=260) (GEM05;) induction therapy of VMP vs. VTP for 6 cycles with weekly bortezomib, then	Patient samples were analyzed by flow cytometry for ploidy. 232 patients with FISH data: 188 were considered standard risk by cytogenetics, 44	Response results recently published in <i>Lancet Oncology</i> . Hypodiploidy is associated with poorer prognosis. DNA ploidy analysis found hyperploidy in 132 (59%) of patients and non-hyperdiploidy (which included hypodiploidy due to small numbers of patients with this abnormality) in 92

	each group split to maintenance with either VT or VP	(19%) high risk, with t(4;14) and del 17 p; the high-risk group also had slightly higher $\beta$ 2M and advanced stage of disease	patients. After induction therapy there were no significant differences in efficacy and similar responses were seen after maintenance; there were no differences seen between VT vs. VP maintenance. PFS from the first and second randomizations were similar, but OS was significantly shorter in the non-hyperdiploid patients; it was 63% at 3 years, and the difference was more pronounced for VTP induction. With bortezomib-based combinations, the RR and CR rates are similar between high- and standard-risk cytogenetics, but this does not overcome the poor prognosis of high-risk cytogenetics in terms of PFS and OS.
<b>Abstract 445</b> A. Broyl	HOVON-65/GMMG-HD 4 (HD4) trial, n= 832 n = 570 bone marrow for plasma cell (PC) purification, n = 341 PC samples had a purity of over 80%	clusters of patients were defined based on translocations: CD-1, CD-2, MS, and MF; 2 hyperdiploid clusters: HY and PR; a low bone sub-cluster: LO; a myeloid cluster; 2 novel clusters CTA and PRL3. GEP was used to determine a high risk signature. The HD4 trial samples were used as a training set. Two independent data sets were used as external validation: UAMS patients on TT2 (n=351) and on TT3 (n=208)	Bortezomib overcomes poor prognosis associated with some clusters. Probes selected from HD4 were those most likely to detect high risk patients. The HD4 high risk signature was validated in two independent data sets and identified a proportion of patients with significantly lower survival irrespective of treatment and whether newly diagnosed or with relapsed disease. The predominant 1q and 1p aberrations in the UAMS set are not seen in the HD4 set, and there seems to be little or no overlap. Patients with a higher hazard ratio were also found in the APEX trial data set, but more work is needed for better prediction.
<b>Abstract 781</b> M. Cavo	post-hoc analysis of two GIMEMA trials of bortezomib-based induction treatments for newly diagnosed patients, n=813; after excluding 223 patients treated with TD, 590 patients received bortezomib; bone marrow PC at diagnosis were isolated using CD138-coated magnetic beads to purity in excess of	218 were transplant eligible and received 5 cycles of VTD induction and consolidation after ASCT. There were 372 transplant-ineligible patients, of whom 181 received VMP for 9 cycles and 191 received VMPT for 9 cycle	Of the total 590 patient population, 261 (44%) had no cytogenetic abnormalities; 175 (30%) had del 13 q and 154 (26%) had t(4;14) with or without del 17p. The high-risk population was subdivided in to those with t(4;14) with or without del 13. The three risk groups were evenly distributed across the three treatments (VTD, VMP, and VMPT). The high-risk group had a significantly higher frequency of higher ISS stage, and other demographic characteristics were generally same, age and $\beta$ 2M. When stratified by cytogenetic abnormalities, those with t(4;14) had shorter survival and lower PFS than those with no cytogenetic abnormalities. Patients with both t(4;14) and

	<p>90%. For the analysis, baseline data on del 13, t(4;14), and del 17 p had to be available</p>		<p>del 17p tended to have shorter PFS than those with one abnormality, but survival for those with either or both was about the same at 18 months. For patients with t(4;14) with and without del 17p, PFS was significantly higher if they were treated with VTD vs. TD. There was no difference in survival between treatment with VMPT vs. VMP. Bortezomib-based regimens were likely to overcome poor prognosis related to several high-risk cytogenetic abnormalities, particularly t(4;14). There were only small numbers of patients with del 17p, so the difference in response was less clear, but regimens containing combinations of three or four drugs might help; however, this is speculation.</p>
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### Hevylite® Test

**The Ratio of Monoclonal to Polyclonal Immunoglobulins Assessed with the Hevylite® Test Predicts Prognosis, is Superior for Monitoring the Course of the Disease, and Allows Detection of Monoclonal Immunoglobulin in Patients with Normal or Subnormal Involved Immunoglobulin Isotype (Abstract 4038)**, was presented by Heinz Ludwig, Department of Medicine, Wilhelminenspital, Vienna, Austria. The Hevylite® test was used to determine the ratio of monoclonal to isotype-matched polyclonal immunoglobulins (heavy/light chain ratio; HLC ratio) at baseline and to evaluate response in 133 patients with myeloma who had normal or below normal levels of the involved immunoglobulin isotype. Conventional prognostic factors were also measured, including IgG, IgA,  $\beta$ 2M, FLC, LDH, and creatinine. Survival analysis and Cox proportional hazards were performed. The HLC ratio is highly prognostic, improves detection of variations in the course of the disease, and increases the diagnostic accuracy in patients with normal or subnormal levels of the involved isotype, including those with negative immunofixation (IFE). Note that The Binding Site, manufacturer of the Hevylite® test, is awaiting a pre-IDE (Investigational Device Exemption) decision from the US FDA for Hevylite® diagnosis and monitoring claims. Dr. Avet-Loiseau has looked at progression-free survival (PFS) for 338 patients on IFM trials using traditional ISS classes based on  $\beta$ 2M plus albumin vs.  $\beta$ 2M plus the Hevylite® ratio. ISS class results fall in 2 prognostic groups: ISS Stage I, which has significantly longer PFS, vs. Stage II + III. The  $\beta$ 2M plus Hevylite® ratio scoring system showed a much lower p-value for separation of these two prognostic groups.

## Conclusions

The trend of increased survival for patients with myeloma that began in the era of novel agents (bortezomib, lenalidomide, and thalidomide) is continuing. The novel agents are now part of new standards of care, with “novel-er” agents in development and early and late clinical trials, and include targeted therapies. Future regimens are likely to be based on combination therapies with unique mechanisms of action and non-overlapping toxicities. Risk stratification and tailoring of therapy to individual patients’ needs is advancing, and is including patient quality of life.