INTERNATIONAL MYELOMA FOUNDATION

ASH 2011
Multiple Myeloma Highlights

Summaries of Multiple Myeloma Presentations from the 53rd Annual Meeting of the American Society for Hematology (ASH) held in San Diego, California December 10–13, 2011

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ASH 2011 Summaries of Multiple Myeloma Presentations

ASH 2011 brought the greatest number of abstracts on multiple myeloma (MM) ever published in the meeting's history, 712 abstracts to be exact. While no single abstract made headlines, taken collectively they offer ample evidence of a year of significant steps forward in understanding, prognosticating, imaging, treating, and monitoring this disease. To better categorize the meeting's highlights, we turn to the IMF's 10 STEPS TO BETTER CARE™ as a framework.

1. Know What You're Dealing With

Several important abstracts were presented in this general category of diagnosis and disease definition, notably a series of studies from the Mayo Clinic, Rochester, MN, USA, that examine outcomes among various subgroups of patients.

Shaji Kumar examined the outcomes of patients in the US, Europe, and Korea who became refractory to both bortezomib and an immunomodulatory agent. He points out that these "double refractory" patients have a poor prognosis no matter where they are treated, with median overall survival at 13 months in the US, 7 months in Europe, and 8 months in Korea. Patients in the US are likely to have more therapies both before and after they become refractory.

- Differences in patterns of therapy and outcomes among patients in the US, Europe, and Asia (Dr. Shaji Kumar, Mayo Clinic, Rochester, MN, USA, abstract #3989)

Vishal Rana's study looking at the reasons for early mortality among those who died within twelve months of diagnosis concludes that advanced age, poor performance status, high ISS stage, and high levels of serum calcium are predictors of early death. Identifying these factors up front will enable doctors to design risk-adapted, appropriate therapy.

- Factors predicting early mortality in patients with newly diagnosed multiple myeloma (Vishal Rana, Mayo Clinic, Rochester, MN, USA, abstract #3981)

Soo-Mee Bang retrospectively examined outcomes in patients over 70 years of age, concluding that exposure to novel agents has improved their overall survival, although it still lags behind that of younger patients.

- Treatment patterns and outcomes in elderly patients (Soo-Mee Bang, Mayo Clinic, Rochester, MN, USA, abstract #3980)

Prashant Kapoor's analysis of survival among patients 45 years of age or less at the time of diagnosis in the era of novel therapies concludes that younger patients not only benefit from the survival advantage granted by their youth and general good health, but from exposure to novel agents, as opposed to their historical controls.

- Survival outcome of young myeloma patients in the era of novel therapy (Prashant Kapoor, Mayo Clinic, Rochester, MN, USA, abstract #2950).

Another significant presentation in this category was the follow-up on the study of therapy for high-risk smoldering multiple myeloma (SMM) by Maria-Victoria Mateos, of the University of Salamanca, Salamanca, Spain. Dr. Mateos's longer-term data now indicate that time to progression to active MM was significantly prolonged in the group of patients with high-risk smoldering disease that was treated with nine cycles of lenalidomide (Revlimid®) and dexamethasone followed by lenalidomide maintenance. The median time to progression to active disease in the untreated group was 25 months, whereas the median has not been reached in the treated group. Only two patients developed second primary malignancies in the treated group, and both malignancies were confirmed to have originated before the start of len/dex therapy. While there is a trend to improved overall survival in the treated group, it is too early to fully assess overall survival benefit, and therefore it is too early to change clinical practice based on these trial results.

- Smoldering myeloma (SMM) at high risk of progression to symptomatic disease (Maria-Victoria Mateos, Hospital Clinico Universitario, Salamanca, Spain, abstract #991).

2. Tests You Really Need

Data in the category of valuable prognostic tests includes the new heavy/light chain assay, genetic studies, imaging studies, and flow cytometry. Of particular note is the identification of an IMiD-binding protein on the surface of MM cells, cereblon, which corresponds to response to treatment with IMiD therapies.

- Cereblon Expression Is Required for the Anti-Myeloma Activity of Lenalidomide and Pomalidomide (Yuan Xiao Zhu, Mayo Clinic, Scottsdale, AZ, USA, abstract #127)

- High Expression of the Thalidomide-Binding Protein Cereblon (CRBN) Is Associated with Improved Clinical Response in Patients with Multiple Myeloma Treated with Lenalidomide and Dexamethasone (Daniel Heintel, University Hospital Vienna, Vienna, Austria, abstract #2879)

Elena Zamagni's prospective study confirms that PET-defined CR is an independent prognostic factor in MM patients treated with up-front novel therapies and autologous transplant. Jens Hillengass from the Heidelberg group reports that the number of focal lesions on whole-body MRI has prognostic value after autologous transplant, but not at diagnosis. Whole-body MRI is not able to discern focal lesions with active MM cells as opposed to osteolyses without active MM.

- Conventionally-Defined and PET/CT-Defined Complete Response (CR) to Novel Agent-Based Induction Therapy and Autologous Stem-Cell Transplantation (ASCT) In Multiple Myeloma (MM): A Prospective Study of Clinical and Prognostic Implications (Elena Zamagni, University of Bologna, Bologna, Italy, abstract #826)
- Prognostic Significance of the Number of Focal Lesions in Whole Body Magnetic Resonance Imaging Before and After Autologous Stem Cell Transplantation (Jens Hillengass, University of Heidelberg, Heidelberg, Germany, abstract #1812)

The serum heavy/light assay, which Heinz Ludwig describes as a "simple test," is able to measure the relationship between clonal and non-clonal protein in the blood. It increases diagnostic accuracy by allowing the measurement of paraproteins that cannot be measured via other techniques, especially in the case of IgA, which tends to migrate to the beta region with serum protein electrophoresis. It can also identify those patients who are not in true CR, despite evidence to the contrary with immunofixation electrophoresis (IFE).

- Serum Heavy/Light Chain and Free Light Chain Measurements Provide Prognostic Information, Allow Creation of a Prognostic Model and Identify Clonal Changes (clonal tiding) Through the Course of Multiple Myeloma (MM). (Heinz Ludwig, University Hospital Vienna, Vienna, Austria, abstract #2883)

Herve Avet-Loiseau compared data from whole exome sequencing and cytogenetics and discovered that there was no significant correlation between recurrent chromosomal changes and gene mutations. There was also no correlation between the number of genetic mutations and cytogenetic risk. In his study of chromosomal abnormalities in MM patients >65 years, he discovered a much lower incidence of t(4;14) in this group, but no significant difference in the occurrence of del(13) or del(17p). As in younger patients, both t(4;14) and del(17p) negatively affect PFS and OS in elderly patients.

- Gene Mutations Detected by Whole-Exome Sequencing and Recurrent Cytogenetic Abnormalities Are Independent Events in Multiple Myeloma (Herve Avet-Loiseau, University Hospital, Nantes, France, abstract #1816)
- Incidence and Prognostic Value of Chromosomal Abnormalities in Elderly Patients with myeloma: The IFM Experience on 1095 Patients (Herve Avet-Loiseau, University Hospital, Nantes, France, abstract #994)
- SNP-Based Mapping Arrays Reveal High Genomic Complexity in Monoclonal Gammopathies: From the MGUS to Myeloma Status (Lucia Lopez-Corral, University Hospital Salamanca, Salamanca, Spain, abstract #295)
- Combining Information Regarding Chromosomal Aberrations t(4;14), Del(17p13) and the Copy Number of 1q21 with the International Staging System Classification Allows Stratification of Myeloma Patients Undergoing Autologous Stem Cell Transplantation: Results From the HOVON-65/GMMG HD4 Trial (Kai Neben, University Hospital Heidelberg, Heidelberg, Germany, abstract #332)
- A 41-Gene Signature Predicts Complete Response (CR) to Bortezomib-Thalidomide-Dexamethasone (VTD) As Induction Therapy Prior to Autologous Stem-Cell Transplantation (ASCT) in Multiple Myeloma (Carolina Terragna, University of Bologna, Bologna, Italy, abstract #805)

Roberto Pessoa Magalhaes of the Salamanca group performed a novel flow cytometric analysis of patients with long-term disease control. He reported that these patients have increased numbers of cytotoxic T-cells and CD56 natural killer (NK) cells.

- Multidimensional Flow Cytometric (MFC) Analysis of the Immune System of Multiple Myeloma (MM) Patients Achieving Long Term Disease Control (Roberto Pessoa Magalhaes, University of Salamanca, Salamanca, Spain, abstract #810

3. Initial Treatment Options

Survival continues to improve for newly diagnosed patients. Better induction therapy improves survival. Jesús San Miguel's 5-year follow-up data on the VISTA trial (VP vs. VMP) demonstrated an overall survival benefit of 13 months,

with a 31% reduced risk of death for those on VMP vs. MP. Although VMP did not overcome cytogenetic risk, patients who relapsed on VMP and went on to other therapy still did better on their second therapy than those on MP did. There was no increased risk of second malignancies with VMP.

- Continued Overall Survival Benefit After 5 Years' Follow-up with Bortezomib-Melphalan-Prednisone (VMP) Versus Melphalan-Prednisone (MP) in Patients with Previously Untreated Multiple Myeloma, and No Increased Risk of Second Primary Malignancies: Final Results of the Phase 3 VISTA Trial (Jesús San Miguel, University Hospital Salamanca, Salamanca, Spain, abstract #476)

Philippe Moreau of the IFM presented data on the PK and PD of subcutaneous bortezomib (Velcade®), demonstrating that it has similar pharmacokinetics and pharmacodynamics to intravenous bortezomib. Site of injection (thigh or abdomen) had no impact.

- Pharmacokinetics (PK) and Pharmacodynamics (PD) of Subcutaneous Versus Intravenous Administration of Bortezomib in Patients with Relapsed Multiple Myeloma: Effects of Subcutaneous Injection Site and Concentration, and Patient Characteristics (Phillippe Moreau, University Hospital, Nantes, France, abstract #1863)

Ruben Niesvizky's UPFRONT study comparing VD, VTD, and VMP in nearly 500 newly diagnosed patients age >65 years in the community practice setting demonstrated that there is added toxicity and no significant benefit to triplet therapy in an elderly population. There were increased rates of hematologic toxicity with melphalan added to Velcade and dexamethasone, and thalidomide increased the incidence of peripheral neuropathy. Similarly, Rachid Baz's retrospective study of doublets vs. triplets of novel agents indicated that patients without high-risk cytogenetics had no difference in OS regardless of whether they had two-drug or three-drug regimens. Those with high-risk cytogenetics, however, had worse survival with the intensive three-drug regimens than with two-drug combinations.

- Efficacy and Safety of Three Bortezomib-Based Combinations in Elderly, Newly Diagnosed Multiple Myeloma Patients: Results From All Randomized Patients in the Community-Based, Phase 3b UPFRONT Study (Ruben Niesvizky, Weill Cornell Medical College, New York, NY, USA, abstract #478)
- Outcomes Analysis of Doublets of Novel Agents with Corticosteroids Versus Regimens with 3 or More Agents for Multiple Myeloma (MM): A Retrospective Analysis (Rachid Baz, Moffitt Cancer Center, University of South Florida, FL, USA, abstract #1878)

Nikhil Munshi, of the Dana-Farber Cancer Institute in Boston, reinforced the theme of "less is more" in the elderly population with his study confirming the efficacy and tolerability of once-weekly bortezomib with dexamethasone.

- Once a Week Bortezomib with Dexamethasone Is Effective with Limited Toxicity in Newly Diagnosed Multiple Myeloma Patients with Older Age and Co-Morbidities (Nikhil Munshi, Dana-Farber Cancer Institute, Boston, MA, USA, abstract #3964)
- The Improved Efficacy of Bortezomib-Containing Induction Regimens (BCIR) Versus Non-Bortezomib Containing Induction Regimens (NBCIR) in Transplant-Eligible Patients with Multiple Myeloma (MM): Meta-Analysis of Phase III Randomized Controlled Trials (Ajay Nooka, Winship Cancer Institute of Emory University, Atlanta, GA, USA, abstract #3994)
- An Alternate Day Dosing Strategy for Lenalidomide in Multiple Myeloma Improves Cost-Effectiveness Whilst Maintaining Efficacy (Rakesh Popat, UCL Cancer Institute, London, United Kingdom, abstract #4201)

4. Supportive Care and How to Get It

Data in this category include details about peripheral neuropathy, venous thromboembolism, renal impairment, and the risk factors for the development of second primary malignancies (SPMs).

Paola Tacchetti reviews the experience with bortezomib- and thalidomide- induced peripheral neuropathy (PN). An interesting new finding is the correlation between the likelihood of PN and deregulated expression of genes (GEP) involving nervous system function from assessment of bone marrow plasma cells from patients with VTD-induced PN.

- Bortezomib- and Thalidomide-Induced Peripheral Neuropathy (PN) in Multiple Myeloma (MM): Clinical and Molecular Analysis of 474 Patients Treated with Thalidomide-Dexamethasone (TD) or Bortezomib-TD (VTD) (Paola Tacchetti, University of Bologna, Bologna, Italy, abstract #1821)

In the final analysis of risk factors for venous thromboembolism, the French group noted increased risk in men, with additional risk for smoking and use of erythropoietic agents (Procrit® or Dorbapoietin®). Although prophylaxis is required with IMiD-based therapy, it was not possible to discriminate added value with low molecular-weight heparin (LMWH) versus use of aspirin, although there was a higher risk of bleeding episodes with aspirin use.

- Final Analysis of MELISSE, a Large Multicentric Observational Study to Determine Risk Factors of Venous Thromboembolism in Patients with Multiple Myeloma Treated with Immunomodulator Drugs (Xavier Leleleu, Hopital Claude Huriez, CHRU, Lille, France, abstract #1235)

The group from Greece showed that bortezomib-based regimens act more rapidly than IMiD-based therapy in the setting of renal insufficiency and are therefore the preferred choice in this situation for newly diagnosed patients.

- The Role of Novel Agents on Reversibility of Renal Impairment in Newly Diagnosed Patients with Multiple Myeloma; a Single Center Experience on 112 Patients (Meletios Dimopoulos, University of Athens School of Medicine, Athens, Greece, abstract #3961)

The group from the University of Pittsburgh's careful review of serial bone marrow biopsies demonstrates that the use of lenalidomide does not increase the likelihood of marrow dyspoiesis (MDS [myelodysplastic syndrome]).

- Longitudinal Evaluation of 110 Bone Marrow Aspirates of Multiple Myeloma Patients Treated with Lenalidomide Alone or in Combination with Autologous Stem Cell Transplantation or Alkylators for Early Dysplastic Signs (Sara Monaghan, University of Pittsburgh, PA, USA, abstract #2885)

The next series of papers evaluates the risk of development of second primary malignancies (SPMs) in patients with MM at different disease stages, with different therapies and in a broad range of settings. It is clear that the MM community as a whole has emerged from its period of collective amnesia on this topic of SPMs, which were first noted with the use of melphalan therapy in the 1970s. The risk of SPMs is linked both to host factors such as increasing age, male sex, and prior or family history of cancer, as well as to the impact of treatment. It is important to note that patients can present with an additional second cancer (either hematologic such as MDS or leukemia or a solid cancer such as lung or breast cancer) simultaneous with (or shortly before) the diagnosis of active myeloma. This onset must be distinguished from SPMs that emerge during the course of subsequent therapy. It is helpful to look at the details of each study evaluating particular therapies. There continues to be an increased risk with the use of melphalan as well as the DCEP regimen (in the IFM 2005 study) as well as, possibly, double versus single high-dose melphalan autotransplant. Bortezomib use does not appear to confer any added risk, as noted in the newly presented data (abstracts #2933 and #3972). It is unclear if any of the novel agents confer any definite added risk except possibly lenalidomide when used along with conventional-dose melphalan (eg MPR regimen: abstract #475) or as consolidation immediately after use of high-dose melphalan (IFM 2005 study). Thus, timing and sequencing do seem to be important in adding to any potential underlying host factors. **But, two key points emerge.**

1. Any increased risk of SPMs is clearly offset by substantially improved remission duration (as well as overall survival for some studies). The onset of SPMs has not had a negative impact on overall survival in any of the studies.

2. The development of SPMs is an important aspect of longer survival, especially in more elderly MM patients. Appropriate monitoring and early management are now crucial aspects of ongoing care.

Awareness is key: the amnesia is over! Regular monitoring (once or twice a year), for example utilizing whole body PET/CT scanning, can be a very effective way to assess the ongoing status and risks.

- Long-Term Outcomes and Safety of Continuous Lenalidomide Plus Dexamethasone (Len+Dex) Treatment in Patients (Pts) with Relapsed or Refractory Multiple Myeloma (RRMM) (Meletios Dimopoulos, University of Athens, Athens, Greece, abstract #2929)
- Risk of Second Primary Malignancies (SPMs) Following Bortezomib (Btz)-Based Therapy: Analysis of Four Phase 3 Randomized Controlled Trials in Previously Untreated or Relapsed Multiple Myeloma (MM) (Jesús San Miguel, University of Salamanca, Salamanca, Spain, abstract #2933)
- Second Malignancies in Total Therapy 3 Trials for Newly Diagnosed Multiple Myeloma: Influence of Lenalidomide Versus Thalidomide in Maintenance Phases (Saad Usmani, University of Arkansas for Medical Sciences, Little Rock, AR, USA, abstract #823)
- Risks for Different Neoplasms (DNs) in Multiple Myeloma (MM) Patients May Involve Specific Host-, Myeloma- and Treatment-Related Susceptibilities: Registry Data of 681 Consecutive MM Patients (Martina Kleber, University of Freiburg Medical Center, Freiburg, Germany, abstract #3929)
- Second Malignancies Among Elderly Multiple Myeloma Patients Exposed to Bortezomib and Other Treatments: An Analysis of the US SEER-Medicare Linked Database (Dina Gifkins, Janssen Research & Development, Raritan, NJ, USA, abstract #3972)

- Secondary Primary Malignancies in Patients with Multiple Myeloma Treated with High-Dose Chemotherapy and Autologous Blood Stem Cell Transplantation (Roland Fenk, Heinrich Heine University, Duesseldorf, Germany, abstract #4087)
- Second Primary Malignancies in Newly Diagnosed Multiple Myeloma Patients Treated with Lenalidomide: Analysis of Pooled Data in 2459 Patients (Antonio Palumbo, University of Torino, Torino, Italy, abstract #996)

5. Transplant: Do You Need One?

Transplant, even in this age of highly effective novel therapies, is still of great value in MM and will remain part of the standard of care for younger patients. Two studies that tip the balance toward high-dose therapy and transplant were Antonio Palumbo's randomized comparison of MPR vs. transplant (MEL200) and Lijun Dai's trial of len/dex with and without ASCT. Both studies conclude that although toxicities are higher with high-dose melphalan and stem cell transplant, the data does suggest improved progression-free (Palumbo) and overall (Dai) survival.

- Melphalan/Prednisone/Lenalidomide (MPR) Versus High-Dose Melphalan and Autologous Transplantation (MEL200) in Newly Diagnosed Multiple Myeloma (MM) Patients <65 Years: Results of a Randomized Phase III Study (Antonio Palumbo, University of Torino, Torino, Italy, abstract #3069)
- A Randomized Clinical Trial of Lenalidomide and Dexamethasone with and without Autologous Stem Cell Transplant in Patients with Newly Diagnosed Multiple Myeloma: Interim Study Results (Lijun Dai, University of Pittsburgh, PA, USA, abstract #4142)

Several studies examined the timing, route of administration, and cost of mobilizing stem cells with plerixafor (Mozobil®), demonstrating that it can be given at a more convenient schedule, can be administered intravenously as well as by injection, and that, though costly, it causes fewer problems than cyclophosphamide and thereby reduces hospitalization and overall healthcare costs.

- Temporal Changes in Plerixafor Administration Do Not Impact Hematopoietic Stem Cell Mobilization Efficacy: Results of a Prospective Clinical Trial (R. Donald Harvey, Winship Cancer Institute of Emory University, Atlanta, GA, USA, abstract #2988)
- Phase II Trial of Intravenously Administered AMD3100 (Plerixafor) for Stem Cell Mobilization in Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation Following a Lenalidomide-Based Initial Therapy (Shaji Kumar, Mayo Clinic, Rochester, MN, USA, abstract #2992)
- Cost Analysis of Using Plerixafor Plus G-CSF Versus Cyclophosphamide Plus G-CSF for Autologous Stem Cell Mobilization in Multiple Myeloma Patients Treated At Memorial Sloan-Kettering Cancer Center (MSKCC) (Nelly Adel, Pharmacy, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, abstract #4059)

6. Response Assessment

Bruno Paiva of the Salamanca group identifies a group of patients who require special monitoring and novel treatment strategies after stem cell transplant.

- High-Risk Cytogenetics and Persistent Minimal Residual Disease (MRD) by Multiparameter Flow Cytometry (MFC) Predict Unsustained Complete Response (CR) After Autologous Stem Cell Transplantation (ASCT) in Multiple Myeloma (MM) (Bruno Paiva, University of Salamanca, Salamanca, Spain, abstract #630)

7. Consolidation and/or Maintenance

The notion of continuous therapy for MM has gained credence as the result of several studies examining the role of consolidation and maintenance therapy. PFS was doubled in Antonio Palumbo's follow-up data on the MM 015 MPR-R trial. In Maria-Victoria Mateos's trial using VT or VP maintenance after VTP or VMP, both VT and VP improved the complete response rate from 24% before to 42% after maintenance. The IFM data on up-front VRD followed by ASCT, VRD consolidation, and lenalidomide maintenance led to an impressive stringent complete response (sCR) rate of 38%.

- A Phase 3 Study Evaluating the Efficacy and Safety of Lenalidomide (Len) Combined with Melphalan and Prednisone Followed by Continuous Lenalidomide Maintenance (MPR-R) in Patients (Pts) ≥ 65 Years (Yrs) with Newly Diagnosed Multiple Myeloma (NDMM): Updated Results for Pts Aged 65-75 Yrs Enrolled in MM-015 (Antonio Palumbo, University of Torino, Torino, Italy, abstract #475)
- Thalidomide As Maintenance Therapy in Multiple Myeloma (MM) Improves Progression Free Survival (PFS) and Overall Survival (OS): A Meta-Analysis (Ajay Nooka, Winship Cancer Institute of Emory University, Atlanta, GA, USA, abstract #1855)
- Bortezomib, Lenalidomide, and Dexamethasone

(VRD) Consolidation and Lenalidomide Maintenance in Frontline Multiple Myeloma Patients: Updated Results of the IFM 2008 Phase II VRD Intensive Program (Marielle Roussel, Hôpital Purpan, Toulouse, France, abstract #1872)

- Maintenance Therapy with Bortezomib Plus Thalidomide (VT) or Bortezomib Plus Prednisone (VP) In Elderly Myeloma Patients Included In the GEM2005MAS65 Spanish Randomized Trial (Maria-Victoria Mateos, University Hospital Salamanca, Salamanca, Spain, abstract #477)
- MRC Myeloma IX, 6 Year Median Follow-up (FU) Highlights the Importance of Long-Term FU in Myeloma Clinical Trials and Differential Effects of Thalidomide in High- and Low-Risk Disease (Gareth Morgan, Institute of Cancer Research, London, United Kingdom, abstract #993)

8. Monitoring without Mystery

Saad Usmani from the University of Arkansas provides compelling data on the utility of MRI and PET in predicting PFS and OS. Former IMF grant awardee Marco Ladetto of the University of Torino presented data on the impact of minimal residual disease (MRD) detected by real-time quantitative polymerase chain reaction, and concluded that careful monitoring of increases in MRD can lead to tailored treatment for those most at risk of relapse. In these patients, it is crucial to make response as complete as possible.

- Implications of Serial Magnetic Resonance Imaging and Positron Emission Tomography Scanning for Survival of Untreated Myeloma Patients Treated with Total Therapy 3 (Saad Usmani, University of Arkansas for Medical Sciences, Little Rock, AR, USA, abstract #3082)
- Long-Term Results of the GIMEMA VTD Consolidation TRIAL in Autografted Multiple Myeloma Patients (VEL-03-096): Impact of Minimal Residual Disease Detection by Real Time Quantitative PCR on Late Recurrences and Overall Survival. (Marco Ladetto, University of Torino, Torino, Italy, abstract #827)

9. Relapse: Do You Need A Change in Treatment?

Assessment of relapse with bortezomib and the IMiDs were the topics of two important studies. Carlos de Larrea from the University of Barcelona identified a sub-group of bortezomib-treated patients with poor prognosis due to DNA methylation, while Enrique Ocio of the University of Salamanca concludes that if a patient is resistant to one IMiD, another IMiD can be effective and should be tried.

- Impact of Global and Gene-Specific DNA Methylation Pattern in Relapsed Multiple Myeloma Patients Treated with Bortezomib (Carlos Fernandez de Larrea, University of Barcelona, Barcelona, Spain, abstract #132)
- Reversibility of the Resistance to Lenalidomide and Pomalidomide and Absence of Cross-Resistance in a Murine Model of MM (Enrique Ocio, University of Salamanca, Salamanca, Spain, abstract #134)

10. New Trials

Probably the richest sources of new information at ASH this year were the sessions on results of new drugs in clinical trials. The most promising include the two drugs likely to be approved by the FDA in the next calendar year, carfilzomib and pomalidomide. In Andrzej Jakubowiak's phase I/II frontline trial of carfilzomib in combination with lenalidomide and dexamethasone, 100% of patients had >/= VGPR after 4 cycles, with 71% of patients in CR after 4 cycles, and 79% in nCR/CR after 12 cycles. All patients were able to mobilize and harvest stem cells for future transplant successfully. The IFM and Dana-Farber data with pomalidomide and dexamethasone in relapsed and refractory MM were also impressive. Other very promising results were from the studies of the monocloncal antibody elotuzumab in combination with lenalidomide and dexamethasone; bendamustine, an old drug finding new life in combination with lenalidomide or bortezomib; and the novel proteasome inhibitors MLN9708, given orally, and marizomib, given intravenously. Perhaps most disappointing were the long-anticipated results of two studies of the HDAC inhibitor vorinostat (Zolinza®),which showed only minimal benefit and significant toxicities.

- Final Results From the Bortezomib-naïve Group of PX-171-004, a Phase 2 Study of Single-Agent Carfilzomib in Patients with Relapsed and/or Refractory MM (Ravi Vij, Washington University School of Medicine, Saint Louis, MO, USA, abstract #813)
- Final Results of a Frontline Phase 1/2 Study of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Multiple Myeloma (MM) (Andrzej Jakubowiak, University of Chicago, IL, USA, abstract #631)
- Carfilzomib Combined with Thalidomide and Dexamethasone (CARTHADEX) As Induction Treatment Prior to High-Dose Melphalan (HDM) in Newly Diagnosed Patients with Multiple Myeloma (MM). A Trial of the European Myeloma Network EMN (Pieter Sonneveld, Erasmus Medical Center, Rotterdam, The Netherlands, abstract #633)
- Unfavorable Cytogenetic Characteristics Do Not Adversely Impact Response Rates in Patients with

Relapsed and/or Refractory Multiple Myeloma Treated with Single-Agent Carfilzomib on the 003 (A1) Study (Andrzej Jakubowiak, University of Chicago, IL, USA, abstract #1875)

- The Novel KSP Inhibitor ARRY-520 Demonstrates Single-Agent Activity in Refractory Myeloma: Results From a Phase 2 Trial in Patients with Relapsed/Refractory Multiple Myeloma (MM) (Sagar Lonial, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA, abstract #2935)
- T-Bird (thalidomide, clarithromycin/[Biaxin®], lenalidomide/[Revlimid®], Dexamethasone) Therapy in Newly Diagnosed Symptomatic Multiple Myeloma (Tomer Mark, Weill Cornell Medical College, New York, NY, USA, abstract #2937)
- Preliminary Results of a Phase 2 Study of PD 0332991 in Combination with Bortezomib and Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma (Ruben Niesvizky, Weill Cornell Medical College, New York, NY, USA, abstract #2940)
- Long Term Outcomes of Pomalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma: Analysis 4 Years After the Original Cohort (Joseph Mikhael, Mayo Clinic, Scottsdale, AZ, USA, abstract # 2942)
- Pomalidomide and Dexamethasone in Relapsed Myeloma: Results of 225 Patients Treated in Five Cohorts Over Three Years. (Martha Lacy, Mayo Clinic, Rochester, MN, USA, abstract #3963)
- A Phase I/II Study of Pomalidomide-Cyclophosphamide-Prednisone (PCP) in Patients with Multiple Myeloma Relapsed/Refractory to Lenalidomide (Antonio Palumbo, University of Torino, Torino, Italy, abstract #632)
- Randomized, Open Label Phase 1/2 Study of Pomalidomide (POM) Alone or in Combination with Low-Dose Dexamethasone (LoDex) in Patients (Pts) with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide (LEN) and Bortezomib (BORT): Phase 2 Results (Paul Richardson, Dana-Farber Cancer Institute, Boston, MA, USA, abstract #634)
- ClaPD (Clarithromycin/[Biaxin®], Pomalidomide, Dexamethasone) Therapy in Relapsed or Refractory Multiple Myeloma (Tomer Mark, Weill Cornell Medical College, New York, NY, USA, abstract #635)
- High Response Rates to Pomalidomide and Dexamethasone in Patients with Refractory Myeloma, Final Analysis of IFM 2009-02 (Xavier Leleu, Hopital Claude Huriez, CHRU, Lille, France, abstract #812)
- Phase II Study of Carfilzomib (CFZ) Combined with Other Anti-Myeloma Agents in Relapsed-Refractory Multiple Myeloma (RRMM) - Updates on the UARK Compassionate Use Protocol (Saad Usmani, University of Arkansas for Medical Sciences, Little Rock, AR, USA, abstract #2947)
- Investigational Agent MLN9708, An Oral Proteasome Inhibitor, in Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (MM): Results From the Expansion Cohorts of a Phase 1 Dose-Escalation Study (Paul Richardson, Dana-Farber Cancer Institute, Boston, MA, USA, abstract #301)
- Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 Dose-Escalation Study (Shaji Kumar, Mayo Clinic, Rochester, MN, USA, abstract #816)
- Phase 1/2 Study of Oral MLN9708, A Novel, Investigational Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (Jesus Berdeja, Mayo Clinic, Rochester, MN, USA, abstract #479)
- Phase 1 Clinical Evaluation of Twice-Weekly Marizomib (NPI-0052), a Novel Proteasome Inhibitor, in Patients with Relapsed/Refractory Multiple Myeloma (MM) (Paul Richardson, Dana-Farber Cancer Institute, Boston, MA, USA, abstract #302)
- A Phase 2 Study of Elotuzumab in Combination with Lenalidomide and Low-Dose Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma (Sagar Lonial, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA, abstract #303)
- Elotuzumab in Combination with Lenalidomide and Low-Dose Dexamethasone in High-Risk and/or Stage 2-3 Relapsed and/or Refractory Multiple Myeloma: A Retrospective Subset Analysis of the Phase 2 Study (Sundar Jagannath, Mount Sinai Hospital, New York, NY, USA, abstract #3968)
- Combination of Bendamustine, Lenalidomide, and Dexamethasone (BLD) in Patients with Refractory or Relapsed Multiple Myeloma Is Safe and Highly Effective: Results of Phase I/II Open-Label, Dose Escalation Study (Suzanne Lentzsch, University of Pittsburgh, PA, USA, abstract #304)

- Bortezomib-Bendamustine-Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma (MM) Shows Marked Efficacy and Is Well Tolerated, but Assessment of PNP Symptoms Shows Significant Discrepancies Between Patients and Physicians (Heinz Ludwig, University Hospital Vienna, Vienna, Austria, abstract #2928)
- A Phase 1 Study of Bendamustine and Melphalan Conditioning for Autologous Stem Cell Transplant in Multiple Myeloma (Tomer Mark, Weill Cornell Medical College, New York, NY, USA, abstract #2042)
- BT062, An Antibody-Drug Conjugate Directed Against CD138, Shows Clinical Activity in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma (Sundar Jagannath, Mount Sinai Hospital, New York, NY, USA, abstract #305)
- Vantage 088: Vorinostat in Combination with Bortezomib in Patients with Relapsed/Refractory Multiple Myeloma: Results of a Global, Randomized Phase 3 Trial (Meletios Dimopoulos, University of Athens, Athens, Greece, abstract #811)
- Vantage 095: Vorinostat in Combination with Bortezomib in Salvage Multiple Myeloma Patients: Final Study Results of a Global Phase 2b Trial (David Siegel, Hackensack University Medical Center, Hackensack, NJ, USA, abstract #480)
- Phase II Study of the Pan-Deacetylase Inhibitor Panobinostat in Combination with Bortezomib and Dexamethasone in Relapsed and Bortezomib-Refractory Multiple Myeloma (PANORAMA 2) (Paul Richardson, Dana-Farber Cancer Institute, Boston, MA, USA, abstract #814)
- Update on a Phase III Study of Panobinostat with Bortezomib and Dexamethasone in Patients with Relapsed Multiple Myeloma: PANORAMA 1 (Jesús San Miguel, University Hospital, Salamanca, Spain, abstract #3976)

This overview of the year's ASH highlights also serves as an introduction to the forthcoming International Myeloma Working Group (IMWG) publications, which will update older guidelines and provide new ones in line with the newly presented data. Among the new guidelines will be:

- Dimopoulos and Terpos's update on imaging
- San Miguel's analysis of the best of the new drugs, with reference to their mechanisms of action
- Treatment of patients older than 75 years of age, piloted by Palumbo
- GEP and High-Risk myeloma, by Chng and Munshi
- Risk stratification, by Chng, Durie, Lonial, and Chanan-Khan
- High-risk SMM and diagnostic testing, by Lonial, Kumar, and Rajkumar
- Secondary Primary Malignancies, by Durie and Crowley
- Balloon kyphoplasty and bone health, by Malloy, Kyriakou, and Durie
- ISS and high-dose therapy, by Moreau, Crowley, and Durie
- Role of supportive care agents, by Chanan-Kahn.

We thus anticipate a year of outstanding contributions to the guidelines for better understanding and management of myeloma, and a year that will bring two new agents to the armamentarium of approved drugs to fight it.

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