

ASH 2012

Multiple Myeloma

Highlights

*Summaries of Multiple Myeloma Presentations
from the 54th Annual Meeting and Exposition
of the American Society of Hematology (ASH)
held in Atlanta, Georgia.*

December 8–11, 2012



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ASH 2012 Summaries of Multiple Myeloma Presentations

ASH 2012 brought its usual bounty of more than 700 oral presentations, posters, and publications on multiple myeloma (MM). These studies continue to deepen our knowledge of drugs that have by now become familiar names, and of new molecules and antibodies that hold promise for the future. Our ability to test, image, identify, monitor, and treat MM, and our understanding of its biology, grow ever better. We once again turn to the IMF's 10 Steps to Better Care™ as a framework for highlighting this year's most important take-aways. Please go to ash.myeloma.org in order to view our filmed interviews with presenters from ASH and/or accompanying presentation slides.

Step 1. Know What You're Dealing With.

Improved Survival

Abstract 3972: Continued Improvement in Survival in MM and the Impact of Novel Agents

Shaji Kumar, Mayo Clinic, Rochester, MN

It is encouraging to begin with a poster presentation documenting the continued improvement in overall survival (OS) in MM. Dr. Kumar's data indicates a median OS of 7.3 years among patients in the time period from 2006-2010, an improvement of nearly double that calculated for the period 2001-2005. Looking at survival by age, those older than 65 years increased in 5-year median survival from 31% to 56%, while those 65 years or younger improved in median 5-year survival from 63% to 73%. These data are particularly impressive for older patients, and are due to the impact of novel agents.

MDS/ALL Pre-Treatment

Abstract 1805: Early Myelodysplastic Changes Present in a Substantial Proportion of MGUS and SMM Patients

Neba Korde, National Cancer Institute, National Institutes of Health, Bethesda, MD

Dr. Korde presented a poster of her research on early myelodysplastic changes in monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) patients. A population-based study of 5,652 Swedish patients demonstrates an 8-fold increase in the likelihood of developing myelodysplastic syndrome (MDS) and acute leukemia among MGUS and SMM patients. This information must be factored in when evaluating the incidence of

second primary malignancies such as MDS and leukemia among patients who have been treated with melphalan plus/minus lenalidomide (Revlimid®).

Abstract 934: Development of MDS and Acute Leukemias in Patients with MGUS, A Population-based Study of 17,315 Patients

Linsey Roeker, Mayo Clinic, Rochester, MN

Dr. Roeker used a data base of 17,315 MGUS patients and also determined that patients with plasma cell disorders carry an inherent risk of MDS.

Step 2. Tests you really need.

Step 6. Response Assessment: Is Treatment Working?

Step 8. Keeping Track of the Myeloma: Monitoring without mystery.

Genomics/FISH

Abstract 724: Promiscuous Cryptic Rearrangements of MYC Locus Cis-Dysregulate MYC Expression and Are Present in the Majority of Patients with Hyperdiploid Myeloma

Leif Bergsagel, Mayo Clinic, Scottsdale, AZ

Dr. Bergsagel's research identifies the *MYC* gene locus and its association with progression of MGUS to active MM. The prevalence of *MYC* rearrangements increases with tumor progression, suggesting a role for *MYC* both early and late in tumorigenesis.

Abstract 933: 1p22 and 1p32 Deletions Are Independent Prognosis Factors in Young Patients with Myeloma: the IFM Experience with 1195 Patients

Benjamin Hebraud, Hôpital Purpan, Toulouse, France

This important study reflects the breadth of cytogenetic abnormalities that have an impact on prognosis in MM. While current recommendations are to test for t(4;14), del 17p, and t(14;16), more recent research has demonstrated the significance of genetic aberrations on chromosome 1. Dr. Hebraud *et al.* used fluorescence in situ hybridization (FISH) screening to determine the presence of 1p22 and 1p32, and found that they are negative prognostic

factors for progression-free survival (PFS) and OS. They recommend that testing for 1p22 and 1p32 should be part of the genetic screening for all patients at diagnosis.

Cereblon

Abstract 194: Cereblon Expression Predicts Response, Progression-free and Overall Survival After Pomalidomide and Dexamethasone Therapy in MM

Steven Schuster, Mayo Clinic, Scottsdale, AZ

We first learned about cereblon at ASH 2011, and this year five abstracts deepened that knowledge. Cereblon (CRBN), an E3 ligase protein coded on chromosome 3p, is the direct protein target for thalidomide, lenalidomide, and pomalidomide (the IMiDs). We highlight Dr. Schuster's presentation not only because it is the only oral on cereblon, but because it demonstrates the potential utility of testing for CRBN in the clinical setting. The researchers tested 148 patients for CRBN expression by Gene Expression Profiling (GEP) prior to treatment with pomalidomide/dexamethasone. They discovered that hyperdiploid patients, who have multiple copies of chromosomes, including chromosome 3, have better responses to IMiDs and lower-risk disease. This is the first demonstration of a clinical correlation between CRBN expression and response to an IMiD plus dexamethasone.

Circulating Plasma Cells

Abstract 321: Detection of MM Cells in Peripheral Blood Using High-Throughput Sequencing Assay

Malek Faham, New York University Clinical Cancer Center, New York, NY

Dr. Faham *et al.* assessed a cohort of 46 MM patients using a highly sensitive new technique (LymphoSIGHT) to see if minimal residual disease (MRD) could be detected in peripheral blood rather than in the bone marrow. Patients spanned 79 time points from newly diagnosed to previously treated but high disease load, to low disease load, and were assessed by DNA and RNA. This new assay was able to identify myeloma clonotypes in peripheral blood myeloma cells in 93% of patients.

Abstract 726: Phenotypic, Functional, and Circadian Characterization of Peripheral Blood (PB) Multiple Myeloma Circulating Tumor Cells (CTC)

Bruno Paiva, Hospital Universitario de Salamanca, Salamanca, Spain

Dr. Paiva posed a series of interesting questions about the movement of CTCs from the bone marrow to the peripheral blood and attempted to answer them using multiparameter

flow cytometry, comparing BM plasma cells (BM mPCs) to CTCs. His primary aim was to understand the role of CTCs in MM pathogenesis. Studying the CTCs of 49 symptomatic patients, he determined that CTCs are a sub-clone of BM mPCs but show no signs of being at a different stage of phenotypic maturation. The CTCs showed fewer cytogenetic abnormalities than BM mPCs. They are quiescent, non-proliferative cells, and like hematopoietic stem cells, they are modulated by the circadian rhythm, peaking during patients' resting hours to colonize other sites in the bone marrow. These may be the cells involved in metastasis.

Hevylite®

Abstract 3964: Immunoglobulin Heavy/Light Chain Measurements During Monitoring Provide Prognostic Information of Relapse After Therapy in MM

Mark Drayson, University of Birmingham, Birmingham, UK

Dr. Drayson *et al.* assessed the use of the heavy/light chain assay (HLC) at maximum response to treatment in IgA MM patients in order to detect residual disease and comment on the prognostic value of stringent CR (sCR). Current electrophoretic tests may be inadequate for IgA MM, which co-migrates with other serum proteins in approximately 60% of cases. The researchers took 196 IgA MM patient samples from the MRC IX trial, and compared SPEP, IFE, FLC, and HLC. They presented data suggesting that immunoglobulin HLC ratios may be better markers of residual disease than electrophoretic methods, and that normalization of both FLC and HLC ratios may be more valuable than sCR.

PET

Abstract 2910: 18-FDG PET Focal Lesion and Avidity Suppression as Early as Day 7 Post-Induction Chemotherapy Predicts for Superior Outcome in Newly Diagnosed MM Patients Treated with TT 3 Trials

Saad Usmani, University of Arkansas for Medical Sciences, Little Rock, AR

Dr. Usmani presented data that may demonstrate a way to assess the need for therapy change as early as 7 days after the beginning of therapy. He studied the PET scans of TT3 patients at UAMS and determined that changes in lesions could be seen very early, and that prognosis could be determined by the number of lesions that were PET-avid on day 7 post initiation of therapy. Those with no lesions apparent at that time had the best prognosis; those with up to 3 PET-avid lesions did slightly worse, and those with >3 PET-avid lesions on day 7 had the worst prognosis.

3. Initial Treatment Options.

Kyprolis® (carfilzomib)

Abstract 333: Carfilzomib Combined with Thalidomide and Dexamethasone Is a Highly Effective Induction and Consolidation Treatment in Newly Diagnosed Patients with MM Who Are Transplant Candidates

Pieter Sonneveld, Erasmus University, Rotterdam, Netherlands

This phase II study was conducted to determine the safety, effectiveness, MTD, response rate (RR), and PFS of 50 newly diagnosed patients. FISH and GEP were also performed. As induction, the regimen included carfilzomib 20/27 mg/m² (20 mg/m² days 1,2 only; thereafter 27 mg/m²); on days 1,2,8,9,15,16 of a 28-day cycle, thalidomide 200 mg per day continuously, and dexamethasone 40 mg weekly for 4 cycles prior to stem cell harvest and transplant. The regimen for consolidation varied only in the dosing of thalidomide at 50 mg/day. Peripheral neuropathy (PN) was the most frequent adverse event. Prior to transplant, 60% of patients achieved very good partial response (VGPR); 18% were in complete response (CR). Of those in CR, 55% had high-risk cytogenetics and 45% had standard risk. After transplant and consolidation, the overall response rate (ORR) was 90%, and the CR rate was 35%, with 70% ≥VGPR.

Abstract 445: Results from the Phase II Dose Expansion of Cyclophosphamide, Carfilzomib, Thalidomide, and Dexamethasone (CYCLONE) in Patients with Newly Diagnosed MM

Joseph Mikhael, Mayo Clinic, Scottsdale, AZ

The rationale for this quadruple regimen is based on the worldwide availability and minimal toxicity of the drugs. CTD is an international standard; the addition of proteasome inhibitor carfilzomib was prompted by the need to achieve rapid, deep response prior to stem cell transplant and to avoid overlapping toxicities. Objectives were to determine MTD and response. The results are based on initial phase II dosing of 20/27 mg/m² carfilzomib; 100 mg thalidomide continuously; 300 mg/m² orally once weekly for 3 of 4 weeks, and 40 mg dex orally once weekly in a 28-day cycle. Treatment was for four cycles prior to stem cell harvest. The regimen was highly effective and well tolerated, with 93% of patients responding by cycle 2. PN occurred in 9/38 patients, but was all grade 1. 96% of patients had at least a partial response (PR), with 74% VGPR. Another 20 patients will be enrolled in the second part of the phase II study at 20/36 mg/m² carfilzomib.

Abstract 730: Carfilzomib, Cyclophosphamide, and Dexamethasone (CCd) for Newly Diagnosed MM Patients

Antonio Palumbo, University of Torino, Torino, Italy

This phase II multicenter study in Italy evaluated induction and maintenance therapy with carfilzomib at 20/36 mg/m² in combination with 300 mg/m² orally weekly and dexamethasone 40 mg orally weekly in patients over 65 years of age or transplant ineligible. CCd was given for 9 cycles, followed by carfilzomib monotherapy maintenance until disease progression. By the completion of cycle 9, 23% of patients were in sCR, with 53% of patients in nCR, CR, or sCR. 100% of patients had at least a PR by the end of cycle 9. 77% of patients had ≥VGPR. Grade 1 and 2 anemia was the most common hematologic AE, and over 30% of patients had grade 1 and 2 thrombocytopenia. Almost 45% of patients had gastrointestinal adverse events (AEs) of grade 1 and 2; there were 4 patients with grade 4 GI AEs, including ileum perforation. There was no PN and no venous thrombosis. More than 40% suffered from grades 1 and 2 fatigue. There was no difference in adverse events among patients younger and older than age 75.

Abstract 732: Phase II Clinical and Correlative Study of Carfilzomib, Lenalidomide, and Dexamethasone (CRd) in Newly Diagnosed MM Patients

Neba Korde, National Cancer Institute, National Institutes of Health, Bethesda, MD

This phase II study for newly diagnosed myeloma patients is designed for 45 patients treated with 8 cycles of CRd followed by 1 year of lenalidomide maintenance. MRD is assessed by flow cytometry, PCR, and FDG PET-CT. Dr. Korde reported on the first 28 patients enrolled in the study. Carfilzomib was given at 20/36 mg/m² days 1,2,8,9,15,16 of a 28-day cycle; lenalidomide was given days 1-21; and dexamethasone was given at 20 mg days 1,2,8,9,15,16,22, and 23 in cycles 1-4, and at 10 mg days 1,2,8,9,15,16,22,23 in cycles 5-8. An additional 12 cycles of lenalidomide maintenance at 10 mg/day, days 1-21, was given to patients with stable disease or better. MRD studies are performed at three time points. There has been no grade 3 or 4 neuropathy. The study was designed to terminate if there were any cases of ≥ grade 3 neuropathy, so second stage accrual is taking place. Best responses after 8 cycles are ≥VGPR in 7 of 8 patients. MRD status by flow cytometry revealed that among 10 nCR/sCR patients, all 10 are MRD negative. Severe toxicities were limited, and responses were rapid and deep. Median time to sCR was 4.5 cycles. The best response rate at a median of 7 cycles is nCR/sCR 75%, with ≥PR 95%.

Velcade® (bortezomib)

Abstract 200: Overall Survival Benefit for Bortezomib-Melphalan-Prednisone-Thalidomide Followed by Maintenance with Bortezomib-Thalidomide (VMPT-VT) Versus Bortezomib-Melphalan-Prednisone (VMP) in Newly Diagnosed MM Patients

Antonio Palumbo, University of Torino, Torino, Italy

Dr. Palumbo posed this study as “the best experimental therapy versus the best standard of care.” He was particularly interested in the synergy between a proteasome inhibitor and an IMiD that was introduced in the experimental arm. 511 patients were given 1.3 mg/m² bortezomib by IV weekly; melphalan 9 mg/m² days 1-4 of each 5-week cycle; prednisone 60 mg/m² days 1-4 of each cycle; and thalidomide 50 mg continuously. Maintenance consisted of bortezomib 1.3 mg/m² IV days 1 and 15, and thalidomide 50 mg daily continuously. With 54 months of follow-up, the median PFS is 35 months in the 4-drug arm, with a 42% reduced risk of progression, and a 48% reduced risk to next therapy, as compared to the VMP arm. The median PFS in the VMPT-VT arm was 31.5 months as compared to 17.8 months in the VMP arm. The 4-drug regimen with maintenance therapy offered better control of the disease and an overall survival advantage of 61% at 5 years (median not yet reached) as compared to 51% in the VMP arm. Patients age 65-75 tolerated the regimen better than those older than 75 years. For this elderly population, the regimen may be too toxic. The benefit of this therapy was also more pronounced in patients who did not have high-risk MM. Grade 2 PN was at 5-6%, with grade 3-4 infrequent.

Abstract 2968: Subcutaneous Bortezomib in Combination Regimens in Newly Diagnosed Patients with MM or Systemic AL Amyloidosis: High Response Rates and Minimal Toxicity

Gunjan Shah, Tufts Medical Center, Boston, MA

Dr. Shah performed a retrospective study of 19 newly diagnosed patients with MM or AL at her institution. She determined that with the use of SQ bortezomib in combination regimens, only 5% of patients required dose reductions of bortezomib for thrombocytopenia. No patients had grade 3 or 4 PN.

Abstract 4049: Once-Weekly SQ Bortezomib with Cyclophosphamide and Dexamethasone Is Well Tolerated and Effective as Initial Treatment in Symptomatic MM

David Simpson, North Shore Hospital, Auckland, New Zealand

All newly diagnosed patients at this institution were treated with CyBorD, with weekly dosing of Velcade at 1.6 mg/m², cyclophosphamide at 300 mg/m² by mouth, and dexamethasone 40 mg by mouth. Patients who proceeded to transplant were given VTD consolidation for four cycles. Treatments were well tolerated, and there was only one bortezomib dose reduction during VTD consolidation (peripheral neuropathy). Responses have improved with each cycle of treatment.

MLN 9708

Abstract 332: A Phase I/II Study of Weekly MLN 9708, an Investigational Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated MM

Shaji Kumar, Mayo Clinic, Rochester, MN

MLN 9708 is physiochemically distinct from Velcade®, and is the first oral proteasome inhibitor. It was given in combination with len/dex for 12 cycles followed by maintenance with 9708 alone once weekly until progressive disease or toxicity. Stem cells were collected after 3 cycles. 65 patients have been treated thus far in phase I and phase II. There was one case of grade 3 PN at the recommended phase II dose (RP2D) of 2.23 mg/m². More than half the patients had >8 cycles of therapy, and there was no problem collecting stem cells for transplant. At the time of Dr. Kumar's presentation, 92% of patients had achieved ≥PR, including a VGPR rate of 55% and 23% CR. One patient died of pneumonia on study, and 7 discontinued therapy due to AEs, including rash (which seems to be caused by both MLN 9708 and lenalidomide), GI problems, fatigue, and neutropenia. 88% of the patients in CR were MRD negative. Two phase III trials are currently enrolling patients, one for newly diagnosed and one for relapsed/refractory myeloma.

4. Supportive Care.

Infections

Abstract 945: Multiple Myeloma and Infections, A Population-Based Study Based On 9,610 MM Patients

Cecilie Blimark, Sahlgrenska University Hospital, Gothenburg, Sweden

Dr. Blimark *et al.* examined the Swedish Cancer Registry 1988-2004, with follow-up data on these patients through 2007. Their infection rate was compared to almost 38,000 healthy controls, and it was determined that MM patients' rate of infection not only increased in the age of novel therapies, but was 7 times that of healthy controls. Infections were both viral and bacterial, and occurred most commonly as pneumonia and septicemia in the first year after diagnosis, at a rate ten times higher than the general population. Patients diagnosed and treated in the most recent period studied, from 2000-2004, had twice the risk of infection compared to those treated during 1986-1993. There is concern that novel agents may increase the risk of infectious complications, necessitating trials of prophylactic measures.

Bisphosphonate Therapy

Abstract 4077: Bone Marker-Directed Dosing of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with MM: Final Results of the Z-MARK Study

Noopur Raje, Massachusetts General Hospital, Boston, MA

Dr. Raje reported the final results of a 121-patient open-label study that used levels of urinary N-telopeptide, a marker of bone resorption, to determine if patients could receive zoledronic acid (ZA) every three months instead of monthly. All patients had 1-2 prior years of intravenous bisphosphonate therapy before entering the study. 117 of the patients were assigned to receive intravenous (IV) ZA every 3 months, and 79 of them stayed on that schedule. 40 switched to monthly ZA: 17 had increased N-telopeptide, there were 4 skeletal-related events (SREs), and 20 had disease progression. There were more AEs among the 40 patients who had ZA monthly. The rate of osteonecrosis of the jaw (ONJ) was 3.3%. The SRE rate was 5.7% the first year and 4.5% the second year. The researchers concluded that it is feasible and safe to give bisphosphonate therapy every three months, although we don't yet know if urinary N-telopeptide is the best marker to use.

Second Primary Malignancy

Abstract 1873: Risk of Second Primary Malignancies in Patients with AL Amyloidosis Treated with Lenalidomide

Vatsbali Sancharawala, Boston University School of Medicine, Boston, MA

Unlike the reports of SPMs in patients with MM who were treated with melphalan and lenalidomide, this *post hoc* study of 82 AL amyloidosis patients treated with lenalidomide at Boston Medical Center did not find an increased rate of second primary malignancies (SPMs). All patients were treated with prior melphalan, either in high-dose therapy with stem cell transplant, or in oral form. The median number of cycles on lenalidomide was 9. With 92 months of follow-up, there was only one case of an invasive cancer: a metastatic lung cancer in a patient who was a smoker. There were no cases of hematologic cancer of lymphoproliferative disorders. The incidence of invasive cancer in the AL patients was 0.44 per hundred patient years, as opposed to the general population's rate of 1.3 per hundred patient years. While longer follow-up may be necessary to ascertain these results, it appears that the use of lenalidomide therapy following melphalan does not increase the risk of SPMs in AL amyloidosis patients.

Abstract 2964: Efficacy and Safety Profile of Long-Term Exposure to Lenalidomide in Relapsed MM

Guillemette Fouquet, Hopital Claude Huriez, Lille, France

Dr. Fouquet *et al.* reviewed the medical records of 50 patients with relapsed/refractory MM who were treated with len/dex for two years or longer. Three patients developed a SPM: one with cancer of the larynx, one with lung cancer, and one with MDS. The SPMs occurred at a median of 4 years after the start of lenalidomide. None of the patients with more than three years exposure to lenalidomide had a SPM. 62% of patients remained on lenalidomide beyond 3 years, reflecting a good safety and tolerability profile. There was no increase in long-term side effects, including SPM.

5. Transplant.

There were not many oral sessions on transplant in MM this year, but many poster presentations brought forth new ideas for tweaking conditioning regimens and assessing risk in transplant patients. We highlight three important studies, two of them concerning allogeneic transplant and a third assessing the role of bortezomib in high-risk patients undergoing autotransplant.

Allogeneic Transplant

Abstract 3116: Allogeneic Hematopoietic Stem Cell Transplantation in First-Line High-Risk MM Patients: Evolving Strategies with the Immunomodulating Drugs

Mauricette Michallet, Centre Hospitalier Lyon Sud, Pierre Benite, France

Much discussion has taken place among researchers around the concept of treating high-risk MM patients with allo transplant as a front-line therapy rather than waiting for late relapse. Dr. Michallet *et al.* performed an important study in which they divided high-risk patients into two groups, one of which received auto/mini allo followed by bortezomib and donor lymphocyte infusion (DLI), and the other of which received auto/mini allo alone, and then compared the two groups to matched patients in prior studies who did not receive allo transplant. Their results demonstrated significantly improved PFS and OS among the patients treated with auto/mini allo followed by immunomodulatory therapy with bortezomib plus DLI.

Abstract 3064: Lenalidomide Is Effective Therapy for Relapse After Allogeneic Stem Cell Transplant for MM

William Bensinger, Fred Hutchinson Cancer Research Center, Seattle, WA

Dr. Bensinger's study demonstrated the efficacy of lenalidomide given to patients who have relapsed following allogeneic transplant. Because a prior study using lenalidomide as maintenance therapy post-allo transplant had caused unacceptable rates of graft versus host disease (GVHD), there had been a general feeling that lenalidomide was not an option following allo transplant. This trial demonstrated that it is possible to capitalize on the new immune system generated by the donor's cells without causing high rates of GVHD. Lenalidomide was given to 18 patients who had relapsed from 2 months to several years after their allo transplants. It was given as monotherapy – without dexamethasone – at 25 mg per day for 21 out of 28 days; a small number of the patients were taking low-dose prednisone for GVHD. There

was one death due to GVHD that occurred after the start of lenalidomide, and dose reductions were necessary for those patients with cytopenias, rash, or infections. 16 of the 18 patients tolerated the lenalidomide well. OS at 3 years was 70%. The median PFS was 14 months. After 5 years, 5 patients remain on lenalidomide.

Autotransplant

Abstract 749: Impact of Bortezomib Incorporated Into Autotransplantation On Outcomes of MM Patients with High-Risk Cytogenetics: An Integrated Analysis of 1894 Patients Enrolled in Four European Phase III Studies

Michele Cavo, Bologna University School of Medicine, Bologna, Italy

Dr. Cavo analyzed data from four large European phase III trials in which patients were treated with induction regimens containing bortezomib before single or double autotransplant. In 3 of the trials, bortezomib was also given as either consolidation or maintenance therapy following transplant. Baseline FISH data at diagnosis was available for 1894 of the 2169 patients enrolled in these trials; high-risk patients were defined as having del 13q, del 17p, and/or t(4;14). The analysis revealed that bortezomib incorporated into either single or double autotransplant significantly increases duration of complete response throughout the treatment program, and confers longer PFS for the overall patient population as well as for some high- and low-risk cytogenetics patient subgroups. The single factor most beneficial to patients with 17p deletion is tandem autotransplant. The addition of bortezomib to the autotransplant treatment plan did not fully overcome the poor risk conveyed by t(4;14) and/or deletion 17p. More mature data is needed for OS follow-up.

Step 7. Consolidation and/or Maintenance.

Maintenance Therapy

Abstract 334: Maintenance Therapy After Stem-Cell Transplantation for MM with Bortezomib/Thalidomide Vs. Thalidomide Vs. alfa2b-Interferon: Final Results of a Phase III Pethema/GEM Randomized Trial

Laura Rosinol, Hospital Clinic de Barcelona, Barcelona, Spain

All patients in this large, randomized Spanish trial were given VTD induction followed by autotransplant. The results of the maintenance phase of the trial, comparing alpha 2b interferon (given SQ three times a week at a dose of 3 MU)

with thalidomide alone (given at 100 mg daily) and with thalidomide plus bortezomib (thalidomide 100 mg daily plus one cycle of bortezomib at 1.3 mg/m² on days 1, 4, 8, and 11 every 3 months), were presented at ASH. Toxicity is an important quality of life factor in maintenance studies, and all three regimens caused some degree of adverse events (AEs). The most common AE with interferon was neutropenia; with thalidomide, PN; and with VT, thrombocytopenia. The CR rate was improved by 15% with thalidomide, by 17% with alpha 2b IFN, and by 19% with VT. While PFS was significantly longer with VT than with the other two maintenance regimens, OS was not significantly different among the three arms at a median follow-up of almost three years, nor was the incorporation of bortezomib able to overcome the impact of poor-risk cytogenetics.

Step 9. Treatment At Relapse.

Step 10. New Clinical Trials.

As is always the case at ASH, there were many presentations involving therapies new and old to treat relapsed/refractory MM. Myeloma remains a highly active area of study with a rich trove of new therapies, many of which will become part of the approved armamentarium over the coming years. The following look to be most promising.

Pomalidomide

There were 7 presentations on combination therapies with pomalidomide for relapsed/refractory myeloma, all with excellent results:

- pomalidomide + carfilzomib + dexamethasone
- pomalidomide + cyclophosphamide + prednisone
- clarithromycin + pomalidomide + dexamethasone
- pomalidomide + dexamethasone
- pomalidomide + cyclophosphamide + dexamethasone
- pomalidomide + bortezomib + dexamethasone.

Among this group, highlights were:

Abstract 74: A Multi-Center Phase I/II Trial of Carfilzomib and Pomalidomide with Dexamethasone (Car-Pom-d) in Patients with Relapsed/Refractory MM

Jatin Shah, MD Anderson Cancer Center, Houston, TX

Dr. Shah reported on the phase I portion of this multi-center phase I/II trial. The MTD was determined to be 20/27 mg/m² carfilzomib days 1, 2, 8, 9, 15, 16; 4 mg pomalidomide days 1-21; and 40 mg dex days 1, 8, 15, 22. The regimen was well tolerated, with only 1 Grade 4 AE (thrombocytopenia),

1 Grade 3 AE (rash), and 1 patient with a neutropenic fever. Patients had been treated with a median of 6 lines of prior therapy and were refractory to lenalidomide. In this heavily pretreated population, the ≥PR rate was 50%, and with minimal responses added in, the clinical benefit ratio was 67%. PFS was 7.4 months, with estimated OS at 1 year of 90%. The phase II portion is currently ongoing with 82 patients enrolled.

Late-Breaking Abstract 6: Pomalidomide in Combination with Low-Dose Dexamethasone: Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase III, Multicenter, Randomized, Open-Label Study

Meletios Dimopoulos, Alexandra Hospital, Athens, Greece

This late addition to the ASH line-up is the data from the MM-003 pom + loDEX vs HiDEX trial that will be presented to the FDA for consideration of pomalidomide's approval. 455 patients were enrolled and randomized to receive either 4 mg pomalidomide days 1-21 plus 40 mg of dex days 1,8,15, and 22 of a 28-day cycle, or 40 mg dex days 1-4, 9-12, and 17-20. Pomalidomide plus low-dose dexamethasone significantly increased PFS and OS compared with high-dose dexamethasone in a population of patients who were refractory to both lenalidomide and bortezomib. Based on the data, the investigators recommend that pomalidomide with low-dose dex should be the standard of care for patients who are refractory to lenalidomide and bortezomib.

Monoclonal Antibodies

In addition to the by now well known first monoclonal antibody used in MM, elotuzumab, there were presentations on early studies of daratumumab (anti-CD 38), BT062 (anti-CD 138), tabalumab (anti-BAFF), and lorvotuzumab mertanise (anti-CD 56). Daratumumab is the most exciting of these promising antibodies, having demonstrated early single-agent activity at last year's ASH.

Abstract 73: Daratumumab, a CD38 Monoclonal Antibody in Patients with MM – Data From a Dose-Escalation Phase I/II Study

Torben Plesner, Vejle Hospital, Vejle, Denmark

Dr. Plesner reviewed the phase I study results, in which concern was taken to assure that the antibody did not cause toxicity to the many other cells in the body in addition to MM cells where CD38 is present. The drug was given to 32 patients in incrementally increased, small doses and for only 8 weeks. To the investigators' surprise, daratumumab proved

to cause little toxicity. Site reactions were the only adverse event, so 25 mg of steroid was added weekly to counteract that problem. The next surprise was that even with only 8 weeks of treatment with this single agent, responses were seen in most patients, including 100% reduction in monoclonal protein in a patient in the 8 mg/kg group. A reduction of 80-100% of the plasma cells in the bone marrow was seen in all groups from 4 mg/kg and up.

Abstract 202: A Phase II Study of Elotuzumab in Combination with Lenalidomide and Low-Dose Dexamethasone in Patients with Relapsed/Refractory MM: Updated Results

Paul Richardson, Dana-Farber Cancer Institute, Boston, MA

This study looked at two doses of elotuzumab, 10 mg or 20 mg given every other week in combination with lenalidomide and dexamethasone. The ORR at 10 mg was 92%, and with 20 mg was 76%, proving that less can be more. Median time to response was 1 month, with time to best response at 2 months. At the 10 mg dose, PFS has not been reached. Adverse events included diarrhea, muscle spasms, fatigue, constipation, and low-grade myelosuppression. ELOQUENT 1 and 2 trials are ongoing, as are other combination trials with elotuzumab.

Proteasome Inhibitors

Two new oral proteasome inhibitors deserve mention here, one from Millennium (MLN9708), maker of bortezomib (Velcade®), and the other from Onyx (ONX0912, or oprozomib), which developed carfilzomib (Kyprolis®).

Abstract 731: MLN9708, a Novel, Investigational Oral Proteasome Inhibitor, in Patients with Relapsed or Refractory Light-Chain AL: Results of a Phase I Study

Giampaolo Merlini, Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

Dr. Merlini presented data on a phase I/II study of this new oral proteasome inhibitor in 22 previously treated patients with relapsed/refractory AL amyloidosis. The MTD was 4 mg given once weekly in a 28-day cycle for up to 12 cycles. ORR was 60%, with grade 3 and 4 adverse events limited to thrombocytopenias. Other side effects were mild. Patients who had CR or better after three cycles remained on single-agent MLN9708; those who had <PR were given MLN9708 with 40 mg of dexamethasone weekly.

Abstract 203: A Phase Ib Dose-Escalation Study of Split-Dose Oprozomib (ONX0912) in Patients with Hematologic Malignancies

Michael Savona, Sarah Cannon Research Institute, Nashville, TN

Dr. Savona presented data from this dose-escalation study of oral oprozomib in a group of heavily pretreated patients with hematologic cancers. Adverse events were gastrointestinal (nausea, vomiting, diarrhea) across all dosing cohorts. Dosing began at 120 mg total per day given in 2 doses 4-6 hours apart for 5 days of a 14-day cycle and escalated in 30-mg increments. Patients received antiemetics, and 4 mg dex was given to those who needed help with nausea. MTD has not been reached, and thrombocytopenia was the only grade 3-4 AE. There was one PR and 1 minimal response (<PR) in patients with MM.

HDAC Inhibitors

Abstract 4061: Rocilinostat (ACY-1215), a Selective HDAC6 Inhibitor, Alone and in Combination with Bortezomib in MM: Preliminary Results From the First-in-Humans Phase I/II Study

Noopur Raje, Massachusetts General Hospital, Boston, MA

Dr. Raje's poster presented data on the first-in-human trial of a selective HDAC inhibitor along with bortezomib and dexamethasone. At the second dose level, they are seeing responses, and there have been no dose-limiting toxicities or serious AEs.

Abstract 1852: PANORAMA 2: Panobinostat Combined with Bortezomib and Dexamethasone in Patients with Relapsed and Bortezomib-Refractory MM

Paul Richardson, Dana-Farber Cancer Institute, Boston, MA

There were several abstracts on panobinostat (4073, 4048, and 4081). Dr. Richardson's abstract 1852 presented data on the fully accrued PANORAMA 2 study combining HDAC inhibitor panobinostat with bortezomib and dexamethasone in 55 patients refractory to bortezomib to see if the drug combination can restore bortezomib sensitivity. Patients also had to have had prior IMiD therapy. 33% of patients had ≥PR. Median duration of response was 6 months. Median OS has not been reached with 8.1 months of follow-up. AEs included diarrhea (71%), fatigue (69%), thrombocytopenia (65%), nausea (60%), anemia (47%), dyspnea (44%), decreased appetite (42%), and peripheral edema (40%).

Others

Other abstracts that feature new drugs to keep an eye on:

Abstract 76: Phase I/II Trial of a Novel CDK Inhibitor Dinacliclib (SCH727965) in Patients with Relapsed MM Demonstrates Encouraging Single Agent Activity

Shaji Kumar, Mayo Clinic, Rochester, MN

2 of 29 patients had deep responses (VGPR) and many others having some degree of drop in M-protein or stable disease. Side effects included GI symptoms, alopecia, fatigue, leukopenia, and thrombocytopenia. Ongoing studies are evaluating different dosing schedules and combination therapy with proteasome inhibitors.

Abstract 78: (and 1857, 2958) Recombinant Circularly Permuted TRAIL (CPT) for the Treatment of Relapsed or Refractory MM: An Open-Label, Multicenter Phase II Clinical Trial

Wenming Chen, Chaoyang Hospital of Capital Medical University, Beijing, China

This is a particularly interesting study because it is the first drug developed for MM in China. In the phase II study 27 patients have been treated with this novel targeted therapy. One patient had a near-complete response (nCR), and 8 patients had PR. AEs included fever, elevation of liver enzymes, leucopenia, neutropenia, rash, thrombocytopenia, and LDH elevation. 3 patients had serious AEs.

Abstract 943 (and 1851, 1855, 2965, 4044): Treatment with Bendamustine-Bortezomib-Dexamethasone (BBD) in Relapsed/Refractory MM Shows Significant Activity and Is Well Tolerated

Heinz Ludwig, Wilhelminenhospital, Vienna, Austria

Bendamustine, an alkylating agent, is marketed in the US for CML as Treanda[®]. In this trial it was successfully combined with bortezomib and dex and produced good results: the ORR was over 65%, with a median PFS approaching 10 months in a heavily pretreated patient population. It is interesting to note that pretreatment with lenalidomide predicted for lower response rate and shorter time to progression. PN, hematologic toxicities, and GI toxicities were reported.

Abstract 449 (and 1868): The Novel KSP Inhibitor ARRY-520 Is Active Both with and without Low-Dose Dexamethasone in Patients with MM Refractory to Bortezomib and Lenalidomide: Results From a Phase II Study

Jatin Shah, MD Anderson Cancer Center, Houston, TX

This kinesin spindle protein inhibitor uses a novel mechanism of action for MM cells, and has no cross-resistance with other anti-MM drugs. It is synergistic with lenalidomide and

bortezomib, and it overcomes dex resistance. All patients on the study were “triple refractory,” that is, refractory to lenalidomide, bortezomib, and dexamethasone, and had at least two prior lines of therapy. 32 patients had monotherapy, and 18 had therapy with ARRY-520 and low-dose dexamethasone. The ORR was 16% (22% in patients who also received dex). Grade 3-4 AEs were neutropenia, thrombocytopenia, and anemia.

Abstract 331: Early Evidence of Anabolic Bone Activity of BHQ880, a Fully Human Anti-DKK1 Neutralizing Antibody: Results of a Phase II Study in Previously Untreated Patients with SMM At Risk for Progression

Nikhil Munshi, Dana-Farber Cancer Institute, Boston, MA

Dr. Munshi *et al.* evaluated single-agent BHQ880 in previously untreated patients with high- and intermediate-risk SMM to see if there was evidence of anti-myeloma activity or bone anabolic activity. Two of the 4 high-risk patients had progressive disease. 22/25 patients remain on the study. There is preliminary evidence of increased vertebral strength at 6 months with quantitative computed tomography. There have been no grade 3-4 AEs.

Abstract 352: Combination Immunotherapy After ASCT for MM Using MAGE-A3/Poly-ICLC Immunizations Followed by Vaccine-Primed and Activated Autologous T-Cells;

Abstract 472: Adoptive Transfer of Gene-Modified T-Cells Engineered to Express High-Affinity TCRs for Cancer-Testis Antigens NY-ESO-1 or Lage-1, in MM Patients Post Auto-SCT

Aaron Rapoport, Greenebaum Cancer Center, University of Maryland, Baltimore, MD

Dr. Rapoport works extensively with genetically engineered autologous T-cells. In the former study with MAGE-A3 vaccine plus costimulated autologous T-cells after autotransplant, 24 of 25 patients were alive at a median of 6 months' follow-up. 1-year event-free survival (EFS) was 77%. At day 180, 53% had CR/nCR. T-cell infusions were well tolerated with no \geq grade 3 toxicity. In the latter study, the first using gene engineered cells (GEC) in MM, it has been established that using GEC after autotransplant is safe, well tolerated, and effective. 3/11 patients had a stringent CR, 7/11 had \geq VGPR, 3/11 had stable or partial responses, and 1/11 had progressive disease. A study using GEC without autotransplant is being planned.

In summary, there was much to learn at ASH 2012, and we have much to look forward to in the coming months and years as our knowledge of MM and the tools to treat it continue to expand.

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