INTERNATIONAL MYELOMA FOUNDATION

ASCO 2011 Highlights for Physicians

ASCO 2011 Annual Meeting Highlights for Physicians

The 2011 Annual Meeting of ASCO (American Society of Clinical Oncology) was held in Chicago, Illinois, USA, from June 3 to 7, 2011.

Summary

- Strategies are being developed to define risk factors in the progression of smoldering (asymptomatic) multiple myeloma (SMM) to myeloma, and to develop therapies to slow or prevent this progression.
- Administration of zoledronic acid may show anti-myeloma activity in addition to reduction of skeletal related events (SRE); however, additional agents active against myeloma bone disease are needed, and some are in clinical trials.
- Most cases of lenalidomide-related second primary malignancies (SPM) appear to be associated with melphalan-based therapies. The low incidence of SPM must be considered within the context of the greater clinical benefit of treatment vs. no treatment of myeloma. Longer follow-up is needed to better identify the risk factors for SPM, including pre-existing malignancies.
- Promising agents in development for myeloma include the proteasome inhibitor carfilzomib and monoclonal antibodies, including elotuzumab.

Diagnosis, Prognosis, Risk Assessment

Smoldering multiple myeloma (SMM)

Ivan Borello, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, discussed **Smoldering and Asymptomatic Myeloma** as part of the Education session entitled **Clinical Problems in the Management of Multiple Myeloma** (eQuestions session). Smoldering multiple myeloma (SMM) is defined by a serum monoclonal protein (M-protein) of at least 3 g/dL and/or at least 10% clonal bone marrow plasma cells (BMPC) in the absence of CRAB criteria (end-organ damage such as hyper**C**alcemia, **R**enal insufficiency, **A**nemia, or **B**one lesions) attributable to the plasma cell disorder. There are about 5000 new cases of SMM per year in the US. The International Myeloma Working Group (IMWG) recommends a baseline bone marrow biopsy and skeletal survey, plus follow-up laboratory tests (in 2 to 3 months to determine rate of progression, then if stable every 4 to 6 months for a year, then if stable every 6 to 12 months). Treatment of SMM is not recommended outside of a clinical trial. Treatment in the context of clinical trials to delay or prevent progression to symptomatic myeloma may be considered for selected patients.

Risk of progression. The risk of progression of SMM (Mayo Clinic data) is 10% per year over the first 5 years, 3% per year over the next 5 years, then 1% per year over the following 10 years. For comparison, the rate of progression of MGUS is 1% per year, suggesting that there are subpopulations within SMM, including those with either slower or more rapidly progressing disease. Therefore, it would be useful to be able to stratify the risk of progression. Two risk stratification studies have been performed. A Mayo Clinic study (N=273) identified the following risk factors: BMPC greater than 10%, M-protein greater than 3 g/dL, and free light chain (FLC) ratio less than 0.125 or greater than 8. The overall risk of progression at 5 years was 25% vs. 51% vs. 76% if 1, 2, or 3 of these risk factors were present. A PETHEMA (Spanish) study (N=89) identified 95% or more abnormal vs. normal plasma cells (decreased expression of CD38, expression of CD56, and absence of CD19 and/or CD45) and immunoparesis (suppression of non-involved immunoglobulin) as two risk factors, with a risk of progression at 5 years of 8%, 42%, or 82% with the presence of 0, 1, or 2 of these factors. It is not known if the progression from MGUS to SMM to myeloma to plasma cell leukemia (PCL) is linear. However, myeloma has been shown to have been preceded by MGUS up to 8 years before diagnosis of myeloma in a retrospective study (Landgren, Blood, 2009). The FLC ratio becomes abnormal closer to the diagnosis of myeloma. There is also a linear increase in M-protein approaching the time to diagnosis of myeloma.

SMM trial results and ongoing trials. Previously published trial results have not shown a survival benefit of early vs. late melphalan plus prednisone or of zoledronic acid in SMM.

- In an ongoing trial of lenalidomide plus dexamethasone, 9 cycles of induction are followed by lenalidomide maintenance, with risk defined by the PETHEMA criteria. Preliminary results (N=118) at a median follow-up of 14 months suggest treatment slows progression and may provide a survival advantage.

- A SWOG observational study of asymptomatic myeloma patients is looking at clinical staging using MRI and PET, genetics, genomics, and immune response until disease progression requiring therapy.
- One gene that has been identified as being associated with progressive myeloma is SOX-2, which is required for self-renewal and pluripotency in embryonic stem cells, and could be a marker for a putative myeloma stem cell. SOX-2 expression is acquired on some CD138 cells in progressive disease, and those patients with MGUS or SMM who have immune recognition of SOX-2 are less likely to have progression to myeloma.
- Another study is evaluating an antibody to KIR (killer-cell immunoglobulin-like receptor, which inhibits natural killer cell activity). [Phase II Trial of IPH2101 (Anti-KIR) in Smoldering Multiple Myeloma (SMM) (NCI-11-C-0024)]

Dr. Borello described potential scenarios for results of early treatment of SMM, which could be so effective it would wipe out those cells responsible for disease progression and lead to a cure. An alternative is that early treatment could effectively reduce the malignant cell population so that maintenance therapy would allow management of progression as a chronic disease. However, there is a risk of early therapy selecting for an aggressive clone, resulting in treatment failure.

Conclusions. Standard treatment for SMM is observation until disease progression. Patients with SMM should be considered for treatment in the context of clinical trials. SMM appears to be heterogeneous, and some subpopulations have a higher risk that could be identified. Early treatment may reduce the risk of progression but could be associated with increased risk of side effects and progression. During the discussion Dr. Borello said that he has seen patients with symptomatic neuropathy (such as peripheral neuropathy) or gait instability and no CRAB symptoms, but there is no evidence that early intervention benefits these individuals. Dr. David Roodman, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA, commented that there are patients with monoclonal gammopathy (MGUS) and neuropathy; usually the antibody is IgG with anti-myelin activity. Plasmapheresis may help in selected patients but often is not beneficial and is risky.

Risk factor assessment and stratification

High-Risk Myeloma was presented by Rafael Fonseca, Mayo Clinic, Scottsdale, Arizona, USA, as part of the Education Session: **Identification and Treatment of the "High Risk Patient" with Non-Hodgkin Lymphoma and Myeloma**. A related manuscript by Dr. Fonseca and Esteban Braggio, "The Use of Genetics Markers and Signatures in Multiple Myeloma Risk Stratification," is available in the ASCO Annual Meeting Educational Book. Dr. Fonseca reviewed publications on risk stratification and treatments associated with differential survival in various risk groups. He pointed out that although many publications suggest identifying higher-risk populations as candidates for more intensive therapies with the goal of CR, this is not necessarily being done in practice, and there are no data to support this approach yet; one strategy being tested is the University of Arkansas Total Therapy modifications based on gene expression profile (GEP) signature. A complication is that previously defined risks may be overcome by newer therapies, e.g., t(4;14) may be overcome at least in part by use of bortezomib. There may be risk factors that have different significances at different stages of disease along the spectrum from MGUS to SMM to newly diagnosed myeloma to first relapse to second relapse to refractory disease to plasma cell leukemia (and finally to human myeloma cell lines). The recent initial sequencing of myeloma genomes has shown that a large number of mutations are not present in all patients. This, Dr. Fonseca says, at the end of the day could mean that myeloma is an "n of one," that is, each individual patient may be unique in risk and response to therapy. Analyses of subclones from individual patients by CGH (comparative genomic hybridization) show changes over time, with new clones appearing and the proportion of clones changing with different treatments during the course of disease. The challenge is to address all the clones to cure the disease.

Other key points are:

- FISH (fluorescence in situ hybridization) is currently the gold standard for identification of high-risk myeloma.
- GEP-based risk stratification correlates moderately with FISH.
- GEP may be an ideal test for patient stratification once it becomes a routine clinical test.

Dr. Fonseca described the Mayo Clinic (Scottsdale) treatment for standard-risk myeloma as induction with CyBOR-D followed by stem cell (SC) collection and transplant (SCT), with lenalidomide maintenance (with or without dexamethasone) at day 100 post-transplant. For high-risk disease, the treatment is RVD induction, SC collection and SCT, then consolidation with CyBOR-D followed by lenalidomide maintenance. He thinks early alkylator-based therapy in high-risk disease might favor the emergence of resistant clones; however, the efficacy of these strategies is still being evaluated.

Generation of an automated tool for querying myeloma transcriptomics for multiple gene expression signatures used in risk stratification (Abstract 8024) was presented by Rafael Fonseca in a poster session. In this study, GEP was performed in purified plasma cells from 469 patients with different stages of myeloma. The results were:

- About a third of patients were identified as having high-risk disease by high proliferation index, high centrosome signature, or high 70-gene index.
- High proliferation index and high centrosome signature significantly correlates with the 70-gene high-risk group.
- Activation of the NF-kB pathway was not significantly different between high- and low- risk subgroups.
- TC subgroups D1 and 11q13 were significantly more common in the 70-gene low-risk group.
- TC subgroups 4p16, Maf, and D2 were significantly more common in the high-risk group.
- Translocations t(4;14)(p16;q32), t(11;14)(q13;q32), and t(14;16)(q32;q23) were 100% predicted by the TC classification.
- IgH translocations without known partner were classified in subgroups D1, D2, 6p21, and Maf.

There is a strong correlation between the most relevant risk-stratification proliferation-based indices and signatures used in myeloma. Although the TC classification is not a very powerful tool for risk-stratification, it is an excellent predictor for the presence of IgH translocations. Multiple variables analyzed simultaneously may provide a powerful research tool for risk-stratification and therapeutic decision-making.

Newly Diagnosed Myeloma

Treatment without Transplant

Survival outcomes in elderly patients with plasma cell myeloma: the three-decade Eastern Cooperative Oncology Group (ECOG) experience (Abstract 8021) was presented by Erica Campagnaro, University Hospitals Case Medical Center, Cleveland, Ohio, USA, in a poster session. This study was a retrospective review of data from 4 phase III ECOG trials in patients (N=1528) with newly diagnosed plasma cell myeloma that did not involve autologous SCT (ASCT): E9846, E5A93, E1A100, and E4A03. The analysis divided patients into three cohorts based on accrual dates (1988 to 1993; 1994 to 2000; and 2001 to 2006). Only patients in the most recent cohort received novel agents (thalidomide plus dexamethasone or lenalidomide plus high- or low-dose dexamethasone), and these patients had a significantly better 5-year overall survival (OS) than patients in either earlier cohort; this difference was more pronounced for patients who were less than age 65 years. Progression-free survival (PFS) was longer for patients younger than age 65 who were treated with novel agents in the most recent cohort, although follow-up time is shorter. PFS for patients older than age 65 years was similar in all three cohorts, that is, novel agents did not appear to contribute to PFS in the older patients. Patients older than age 65 were more likely to have worse performance status and higher creatinine and beta-2-microglobulin (B2M) than younger patients, but there was no difference between age groups in other prognostic factors such as Durie-Salmon stage, C-reactive protein, or hemoglobin.

This poster was discussed by Suzanne Lentzsch, University of Pittsburgh, Pittsburgh, Pennsylvania, USA. She noted that this is an important analysis of only large, randomized trials, and asks an important question about the outcome of older patients. Weaknesses include the lack of analysis of the cause of death (whether due to myeloma or other causes) which would be helpful in determining whether the marginal increase in OS in older patients is due to novel agents or better medical care, e.g., better cardiac care. It is not clear if the difference is due to reduced dosages or less transplant for older patients or unfavorable cytogenetics. It also isn't known if increased OS might be attributed to salvage therapy with bortezomib, and if bortezomib should be given upfront to older patients with adverse cytogenetics. Unresolved issues include:

- Despite more aggressive treatment and ASCT up to age 75 years and the use of novel agents, there has been only a marginal increase in OS in patients over age 65 years.

- PFS has not improved since 2001 in older patients, questioning the effect of improved anti-myeloma treatment.
- Is increased OS in older patients due to better medical care?
- Is the increased risk of adverse cytogenetics associated with worse outcome in older patients?
- Due to the biologic heterogeneity of patients age 65 to 75 years, outcome evaluation should be based on treatment, not on age.
- More information is needed on the biology of myeloma in older patients.

Treatment with Transplant

Melphalan, prednisone, lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) in newly diagnosed multiple myeloma (M) patients: a phase III trial (Abstract 8020) was presented by Mario Boccadoro, University of Torino, Torino, Italy, in a poster session. This study was conducted in patients with newly diagnosed myeloma who were younger than age 65 years. After four induction cycles of lenalidomide plus low-dose dexamethasone, patients were randomly assigned to either MPR (N=202) or MEL 200 with autologous stem cell support (ASCT; N=200). A second randomization assigned patients to either no maintenance or lenalidomide maintenance. Results are summarized in the following table:

Table 1.

	MPR (N=202)	MEL 200 ASCT (N=200)	P value
≥VGPR	60%	58%	0.24
CR	20%	25%	0.49
PFS at 24 months (median follow-up 20 months)	59%	75%	0.005
18 months PFS CR vs. not	90% vs. 66%	87% vs. 76%	N/A
24-month OS	95%	97%	0.18
Grade 3 and 4 neutropenia	55%	89%	<0.001
Grade 3 and 4 infections	0	17%	<0.001
Grade 3 and 4 GI toxicity	0	21%	<0.001
DVT (prophylaxis was randomly assigned: aspirin or LMWH*	2.44%	1.13%	0.43
Second tumors	0.005%	0.005%	N/A

* The incidence of DVT (deep vein thrombosis) was higher with low molecular-weight heparin (LMWH; 40 mg/day enoxaparin) than with aspirin (100 mg/day), but pulmonary embolism (PE) occurred with aspirin and the overall incidence of thromboembolism (TE) was higher with aspirin. CR = complete response; GI = gastrointestinal; VGPR = very good partial response

MEL200 was superior to MPR for PFS, although toxicities were significantly higher. This is the first study to show a PFS advantage for ASCT compared with combination chemotherapy containing a novel agent, although at this time, OS is similar for both treatments, and longer follow-up is needed.

Supportive Care

Bone Disease Overview

David Roodman, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA, presented **Bone Disease and its Management in Multiple Myeloma** as part of the Education Session, **Clinical Problems in the Management of Multiple Myeloma** (eQuestions session). A manuscript associated with this presentation is available in the ASCO Education Book for the meeting. Bone involvement is most frequent in myeloma vs. other cancers, in up to 84% of patients with advanced disease. Any bone can be affected, but bones with higher red marrow content are most often affected, with pathologic fractures occurring most often in vertebrae (70%), followed by ribs (14%), femora (5%), and other bones. At presentation 20% of patients have pathologic fractures, and 60% will have them over the course of their disease. Pathologic fractures in myeloma are associated with decreased survival and increased cost of treatment.

Management strategies include the following:

- Lifestyle modifications such as movement and avoidance of bed rest (although movement may cause pain), calcium supplements, precautions to reduce falls.
- Radiation therapy to treat painful lesions (should be used sparingly because overuse can compromise the use of systemic therapy).
- Surgical interventions: vertebroplasty (no benefit in osteoporosis); kyphoplasty (benefit in patients with cancer, including myeloma).
- Pharmacologic management: vitamin D supplementation (many patients deficient or insufficient, but appropriate levels and dosing are unclear and trials are ongoing); bisphosphonates (inhibit osteoclast activity); treatment of myeloma (bone disease can progress in patients in complete remission).

Bisphosphonates. Pamidronate and zoledronic acid are equally active in reducing skeletal related events (SRE), including fractures, radiation to bone, vertebral compression fractures, and hypercalcemia. Issues include:

- Renal toxicity (renal function must be monitored).
- Osteonecrosis of the jaw (ONJ), although good preventative dental care has reduced the incidence.
- SREs (skeletal-related events) are decreased by 50% and progression of bone disease still occurs, although at a slower rate.

- Antitumor activity of zoledronic acid has been demonstrated in the MRC Myeloma IX trial (updated results are summarized below), although this was seen in patients without as well as with bone disease, the anti-myeloma therapy used was not as intensive as current therapy, and newer agents are active in bone, so Dr. Roodman believes that it isn't clear that all patients should be treated with bisphosphonates.

New therapies and trials. New therapies are still needed for myeloma bone disease. New targets have been identified and are being addressed in clinical trials. Targets include inflammatory proteins; factors produced by myeloma cells such as RANKL and IL-6 that drive osteoclastogenesis (IL-6 is also produced by osteoclasts and stimulates myeloma cells); inhibitors of bone formation produced by myeloma cells like DKK1 and IL-3. RANKL induces osteoclast formation; in myeloma RANKL production is increased and osteoprotegerin (which is bound by syndecan on CD138 cells) is decreased. The imbalance of RANKL and osteoprotegerin results in myeloma bone disease.

The monoclonal antibody **denosumab** binds RANKL highly specifically and inhibits formation and activation of osteoblasts. Denosumab has been shown to be as effective as zoledronic acid in patients with bone lesions associated with breast or prostate cancers in phase III trials. Denosumab has also been tested in a phase III trial vs. zoledronic acid in bone disease associated with solid tumors, with a small number of patients with myeloma included (about 170 of a total of 1600 patients), and is not inferior to zoledronic acid in delaying or preventing first on-study SRE, with an equal incidence of ONJ after 2 years of treatment. This study shows that ONJ is not the result of bisphosphonates per se, but the result of blocking osteoclast activity and bone remodeling. In a phase II trial in myeloma, single-agent denosumab reduces bone resorption markers with no effect on tumor markers. However, denosumab could enhance anti-myeloma agents. A large randomized phase III trial (N=1000) of denosumab vs. zoledronic acid in patients with newly diagnosed myeloma and at least one bone lesion is planned to begin in September, 2011. Denosumab is administered subcutaneously and requires no adjustment for renal function.

DKK1 and sFRP-2 inhibit WNT signaling, a critical pathway in osteoblast differentiation. These inhibitors are secreted by myeloma cells. An anti-DKK1 antibody increases bone formation in an animal model of myeloma and decreases tumor burden. **BHQ880** is an anti-DKK1 human monoclonal antibody that is in an early phase clinical trial in patients with myeloma.

Discussion. Dr. Roodman pointed out that there are no data about holding bisphosphonates before dental procedures, and that this is a legal protection issue. He said it is not necessary to hold bisphosphonates for routine cleaning or other procedures such as fillings or root canals, but bisphosphonates should be held for 2 to 3 months for planned procedures like extractions or surgery. If there is an emergent condition, the procedure should be performed and bisphosphonates held until the socket heals. A lot of bisphosphonates persist in the bones for a long time but are sequestered. Inhibiting bone remodeling will inhibit healing after surgery or extraction. He noted that in the MRC Myeloma IX trial, there was a benefit of bisphosphonates 1 to 4 years post treatment but the incidence of ONJ increases with the dose of zoledronic acid. This group used dental prophylaxis over the follow-up period of thalidomide vs. placebo maintenance suggesting that if there is good dental prophylaxis, bisphosphonates can be administered past 2 years. ASCO guidelines recommend administration for 2 years. Dr. Roodman says that his personal practice, which is not based on data, is to extend the interval of bisphosphonate administration for patients with CR or plateau, but if they have active disease then he treats with bisphosphonates. He notes that because denosumab is an antibody it is reversible; when treatment is stopped there is a rebound of osteoclasts, so patients can be given a "holiday" from treatment. However, the use of denosumab in the US currently is off label and it is not approved for myeloma at this time.

Bisphosphonates in the MRC Myeloma IX Clinical Trial

There were two oral presentations and one poster presentation discussing updates on the use of the bisphosphonates zoledronic acid vs. clodronate in the MRC Myeloma IX clinical trial. Data analyses since the trials reports at ASCO 2010 are summarized in the table below. The trial design and some results have been previously reported. Patients (N=1960) with newly diagnosed myeloma were treated in either an intensive or non-intensive pathway. Within each pathway, patients were randomly assigned to zoledronic acid (n=981) or clodronate (n-970). Patients were further randomly assigned within each treatment group either to maintenance therapy with thalidomide or to no maintenance. Note that although clodronate is not currently approved in the US, it is used in other countries, including Canada and the UK.

Table 2.

Presenter Title Abstract	Results	Conclusions
Gareth Morgan, Royal Marsden Hospital, Leeds, UK, presented for Kevin Boyd. Does zoledronic acid (ZOL) reduce skeletal-related events (SREs) and improve progression-free survival (PFS) in patients (Pts) with multiple myeloma (MM) with or without bone disease? MRC myeloma IX study results. Abstract 8010	SREs were defined as vertebral or other fractures, spinal cord compression, need for radiation or surgery of bone lesions, or the appearance of new osteolytic lesions, (the latter is not usually included in the definition of SRE). About 70% of patients (n=1350) had bone disease at presentation, 30% (n=578) did not. Classically guidelines specify no bisphosphonates if no bone disease, but all patients received bisphosphonates in this trial. Median follow-up was 3.7 years in the zoledronic acid group vs. 3.8 years in the clodronate group. Zoledronic acid significantly reduced the risk of SREs by 26% vs. clodronate (35.3% vs. 27.0% SREs). Zoledronic acid reduced SREs in patients with or without bone lesions at baseline; 24% reduced SRE overall,19% in those with bone disease at presentation, and 42% in those with no lesions at presentation. Zoledronic acid significantly increases OS vs. clodronate in patients with bone disease at baseline; however, OS was similar for zoledronic acid and clodronate for patients who did not have bone lesions at baseline. Increased PFS with zoledronic acid vs. clodronate was bone disease-dependent and seen in both intensive and non-intensive pathways. Patients were also grouped into high vs. low risk [high = t(4;14), t(14;16), t(14;20), del 17, 1q + for both pathways and 1p32 del in the intensive pathway only]. The effect of zoledronic acid is more pronounced in low-risk disease. There were no differences in OS between bisphosphonates by patient sex, ISS state, or disease risk. ONJ was 3% to 4% and no renal signal was seen.	Zoledronic acid significantly reduces the relative risk of SREs vs. clodronate regardless of bone disease status at presentation, SRE rates were higher if there were pre-existing bone lesions at presentation. Zoledronic acid decreases SREs even when new bone lesions were excluded from the SRE composite definition. The decrease in SREs with zoledronic acid was seen within the first year independent of bone disease status at presentation. Zoledronic acid significantly improved OS and PFS vs. clodronate in the overall population, and although the study was not powered to evaluate treatment effects in subpopulations, the OS and PFS benefits appear limited to patients with bone disease at presentation, and were seen in both intensive and non-intensive pathways. Adverse events (AEs) were consistent with those previously observed.
Faith Davies, Institute of Cancer Research, London, UK. Are there benefits to long-term bisphosphonate treatment in multiple myeloma (MM)? Insights from temporal analyses of zoledronic acid (ZOL) versus clodronate (CLO) in the MRC Myeloma IX Trial. [Title on presentation slides: Bisphosphonate treatment in multiple myeloma: should they be used until progression?] Abstract 8011	Data from the MRC Myeloma IX trial were used to see if patients should be given bisphosphonates until disease progression. Over 80% patients were still on randomized bisphosphonate therapy after 3.8 years follow-up. A multivariate analysis was performed to determine which patients were at highest risk for SREs. Zoledronic acid reduced the risk of SRE. A history of bone disease at presentation increased the risk of SRE on treatment. Zoledronic acid may increase time to second SRE vs. clodronate, but the difference is not statistically significant. Zoledronic acid did significantly reduce SREs vs. clodronate during maintenance therapy (n=428 vs. n=390 for zoledronic acid vs. clodronate at the maintenance stage). Zoledronic acid significantly reduces risk of a first SRE vs. clodronate after maintenance randomization independent of the maintenance arm (thalidomide vs. placebo). In a landmark analysis zoledronic acid continued to significantly decrease the incidence of first SRE vs. clodronate after completion of 1 year of treatment. This difference was also statistically significant after completion of 2 years. Beyond 3 years the curves are still separated but not statistically significantly different. At up to 5 years, zoledronic acid continues to be associated with fewer SREs than clodronate. The OS benefit of zoledronic acid becomes significant early in the course of treatment, and increases over time.	Patients initiating therapy for myeloma have an increased risk for SRE, with prior SRE, osteolytic bone lesions, hypercalcemia, and the use of melphalan prednisone increasing this risk. Zoledronic acid significantly decreases SREs vs. clodronate regardless of bone disease status at presentation or of treatment pathway or regimen. The benefits of using zoledronic acid were seen within the first year, supporting early initiation of zoledronic acid. The increased OS benefit of zoledronic acid over clodronate is significant within the first 4 months of treatment and increased over time, including the maintenance portion of the trial, and is seen during each of the first 3 years on study. These analyses support the early initiation of zoledronic acid to prevent SREs and prolong survival, and treatment at least until disease progression to provide a long-term benefit.
Gareth Morgan, Royal Marsden Hospital, Leeds, UK Defining the biological subgroup of multiple myeloma patients which benefits maximally from the overall survival benefit associated with treatment with zoledronic acid Abstract 8083 (poster)	Baseline bone disease was associated with a higher proportion of hyperdiploidy and lower proportions of t(4;14) and maf translocation [t(14;16), t(14;20)] than the overall trial population. Zoledronic acid is superior to clodronate for reducing the risk of SREs independent of SRE status at baseline. t(4;14), t(14;16), t(14;20), 17p del or 1q+ in both treatment pathways, or 1p32 del in the intensive pathway were associated with poor prognosis. In patients with the poor-risk signature, the risk of SREs was no different with zoledronic acid vs. clodronate. Zoledronic acid did reduce SREs in patients in the low-risk subgroup. OS was significantly shorter in patients with bone disease at baseline than without (median 45.5 months vs. 51.6 months, P=0.009). There was no difference between zoledronic acid and clodronate for renal toxicity. ONJ was mild to moderate and significantly less frequent with clodronate.	The benefit of zoledronic acid on OS vs. clodronate is independent of gender and disease stage. Zoledronic acid vs. clodronate: • significantly improved OS in patients with bone disease or other SREs at baseline. • more effectively reduced SREs in patients with and without bone disease at baseline. • significantly reduced risk of SREs in patients with lower-risk but not high-risk cytogenetics.

Results are summarized in Table 2.

Discussion. Abstracts 8010 and 8011 were discussed by David Roodman, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA. He reviewed the major findings in the presentations as well as published results on the effect of bisphosphonates in myeloma and other cancers. He noted that there is no apparent benefit in OS with the use of bisphosphonates in patients who have bone disease at presentation, and that bisphosphonate use will result in additional cases of ONJ (assuming the rate of occurrence is the same in patients with and without bone disease). Therefore, the clinical economic cost of treating all patients with bisphosphonates must be considered. The increased incidence of ONJ at 3 years of treatment (seen in patients with breast cancer) was the basis of the ASCO guidelines suggesting 2 years of bisphosphonate therapy. However, good dental prophylaxis has been shown to decrease the incidence of ONJ.

Important remaining questions include whether using other regimens containing agents that may target bone, like bortezomib or lenalidomide, would obscure the benefits of zoledronic acid on OS in patients with bone disease, and the SRE effects of zoledronic acid in patients without bone disease. Do patients without bone disease need less frequent administration of zoledronic acid (or another bisphosphonate) for the same SRE benefit without increased risk of ONJ? Will the lower incidence of ONJ seen with dental prophylaxis remain low with longer periods of treatment with zoledronic acid?

Question and answer discussion. Dr. Morgan pointed out that because the effect of bisphosphonate treatment on high- vs. low-risk disease wasn't part of the starting hypothesis of MRC Myeloma IX, this effect must be confirmed in a prospective study. Dr. Davies said they are looking at data for the effect of continuous vs. intermittent vs. stopped bisphosphonate administration, but small patient numbers in the subgroups make this analysis difficult. Dr. Morgan said they used skeletal surveys, not DEXA, so they don't know the rates of generalized osteopenia in patients. Menopausal status, which is important in the breast cancer studies, is not important in myeloma bone disease.

Taimur Sher, Roswell Park Cancer Institute, Buffalo, New York, USA (session co-chair) asked how long patients should be treated based on response. Dr. Morgan said they are trying to address this in a subsequent analysis. New osteolytic disease is associated with progression, and there is always a period when bone resorption occurs before relapse. Dr. Roodman said that Dr. Raje is using bone markers to decide on treatment, and agrees these should be used, but more selectively. Patients with breast and prostate cancers benefit at each landmark up to at least 3 years of bisphosphonate treatment. The risk of ONJ should be balanced with benefit. Dr. Davies said that the ONJ risk doesn't seem to increase over time.

Other Supportive Care Issues

In the Education session **Clinical Problems in the Management of Multiple Myeloma** (eQuestions session), Sikander Ailawadhi, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, USA, who was a substitute speaker, presented Complications of Anti-Myeloma Therapies. He discussed the need to be aware of and appropriately manage hematologic and gastrointestinal side effects, thromboembolism, infections (including zoster reactivation associated with bortezomib), fatigue associated with thalidomide, lightheadedness associated with bortezomib, and ONJ. He mentioned guidelines for the management of side effects of novel therapies and steroids developed by the Nurse Leadership Board of the International Myeloma Foundation (IMF) published in 2008 in the *Clinical Journal of Oncology Nursing* and available through the IMF web site. During the discussion, someone asked if bortezomib once a week or administered subcutaneously was the new standard. Dr. Ailawadhi said that this was an important topic. The standard regimen of I.V. bortezomib is administration on days 1, 4, 8, and 11. There are data supporting the weekly administration of I.V bortezomib in combination therapy such as modified VMP or modified CyBOR-D. There has been one non-inferiority study of subcutaneous bortezomib administered on days 1, 4, 8, 11, suggesting it is possible to maintain efficacy with reduced adverse events such as PN [a phase III trial reported by Moreau *et al*. in *Lancet Oncology* 2011, 12:431-440, in which time to progression (TTP) and 1 year OS were similar between the subcutaneous group of 145 patients and the I.V. group of 73 patients, all of whom had relapsed myeloma]. However, subcutaneous bortezomib is not used yet in general practice and is off label.

Response Assessment and Monitoring

Secondary Malignancies

There were three oral presentations and one poster presentation discussing the incidence of second primary malignancies (SPM) in patients with myeloma who had been treated with lenalidomide. These are summarized in the Table 3.

Secondary malignancies following multiple myeloma, Abstracts 8007 to 8009, were discussed by Ola Landgren, National Cancer Institute, Bethesda, Maryland, USA. He reviewed the data and observed that the reporting of SPMs is not perfect, there is under-reporting, the retrospective study format can introduce bias, survival among treatment arms can be different, and there can be variations in how data are collected. SEER data are not broken down by MDS or other specific malignancies. If a patient develops a cancer common in the ageing population, e.g., prostate cancer, does data collection stop? If a patient develops MDS later, is that information collected? Interest in SPMs after myeloma is not new; AML in patients with myeloma was reported in the 1960s and 1970s. In the 1980s MDS/AML was associated with melphalan- but not cyclophosphamide-containing regimens for myeloma. At last year's American Society of Hematology (ASH) meeting, there were reports of the incidence of SPMs in 3 randomized studies involving lenalidomide maintenance, including IFM 2005-02, CALGB 100104, and MM-015, renewing interest in the issue.

Mechanisms. Little is known about the mechanisms, in part because the incidence in untreated patients is not known. However, a Swedish study presented at the International Myeloma Workshop, Paris, 2011, compared the incidence of SPMs in patients with myeloma (N=8740) and MGUS (N=5652) with that in the general population. The risk of developing AML/MDS is about 11-fold higher in patients with myeloma and 8-fold higher in patients with MGUS. The isotype of MGUS plays a role, with IgG and IgA associated with AML/MDS. The level of M-spike is also associated with increased risk. Dr. Landgren proposed a model for SPM after myeloma that takes into account treatment, myeloma-related factors, host-related factors (single nucleotide polymorphisms or SNPs that predispose to both myeloma and SPM), environmental and behavioral factors, and the interaction of all of these.

Clinical implications. Based on small numbers, 3 randomized studies reported at ASH show more hematologic malignancies in the treatment arm. Other studies show a small or no indication of increased risk. The cumulative incidence of

Table 3.

Presenter Title Abstract	Study Patients Follow-up	Results	Secondary primary malignancies (SPM)	Conclusions
Antonio Palumbo, Molinette Hospital, Torino, Italy. Incidence of second primary malignancy (SPM) in melphalan-prednisone-lenalidomide combination followed by lenalidomide maintenance (MPR-R) in newly diagnosed multiple myeloma patients (pts) age 65 or older. Abstract 8007	MM-015 study N=459 in 82 centers in Europe, Australia, and Israel of MPR-R vs. MPR vs. MP. Patients age 65 to 75 years were about 75% of each arm, and there was a higher than usual ISS stage III=high-risk (about 50%). Maintenance in MPR-R. MPR-R n=152, MPR n=153, MP n=154. Median follow-up was 25 months for efficacy and PFS; for SPM and OS median follow-up was 30 months. Retrospective study of 9 EMN trialist group experimental trials in 2459 newly diagnosed patients treated with combination therapies that included cyclophosphamide, lenalidomide, and dexamethasone, e.g., CRD/CPR; MPR; ASCT-R maintenance; VMPT; MP; MPT; and VMP. 1798 patients analyzed in 2 groups with at least 1 year of follow-up: lenalidomide plus alkylating agent vs. no lenalidomide:, others had too short follow-up.	PFS has already been presented; MPR-R was significantly better with an overall 60% reduced risk of progression; for patients age 65 to 75 years there was a 69% reduced risk of progression for MPR-R. PFS in MPR and MP arms drops as soon as treatment stops. Landmark analysis: 65% reduced risk of progression in all patients; over age 75 years: 70% reduced risk of progression with MPR-R vs. MPR. OS in ITT population 70% estimated at 3 years; no difference between arms. The incidence of SPM in the normal: men have a higher rate; in individuals age 65 to 74 years the risk of SPM is 2% per year of life, and the risk increases with age. So SPMs are expected in the normal population. The observed to expected rate of SPM in the Italian cancer registry were also compared.	SPM no difference for all total invasive tumors : 8% vs. 5.9% vs. 2.6% MPR-R vs. MPR vs. MP; or for solid tumors: 3.3% vs. 2.6% vs. 3.3%. For hematologic malignancies there was a difference: 4.7% vs. 3.3% vs. 0.7%, mostly due to increased AML and MDS in lenalidomide arms. But the risk of death due to PD (70%) is much greater than the risk of death due to hematologic and solid tumors (7%). In the comparison of risk of SPM vs. death from myeloma, in all patients SPM risk is 2 to 3% vs. a 40% risk of death; in patients treated with lenalidomide, the risk of SPM is 7% vs. 27% risk of dying of myeloma. With no lenalidomide the risk of SPM is lower but the risk of dying of myeloma is higher at 45%. The observed rate of SPM in all patients was lower than expected from the registry data; in lenalidomide-treated patients the observed SPMs were also lower than expected.	Continuous lenalidomide results in unprecedented PFS improvement. Risk of SPM is increased by use of lenalidomide plus melphalan (not lenalidomide plus dexamethasone). However, the incidence of SPM is low. Benefit to risk strongly favors continuous lenalidomide for patients with newly diagnosed myeloma but current follow-up is about 4 years and longer follow-up is needed. Although the risk of SPM with lenalidomide and alkylating agents is higher than without, the risk of dying of myeloma is lower with lenalidomide and alkylating agents.

Table 3. *(continued)*

Adriana C. Rossi, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, New York, USA. Incidence of second primary malignancies (SPM) after 6-years follow-up of continuous lenalidomide in first-line treatment of multiple myeloma (MM). Abstract 8008	This study looked at newly diagnosed, transplant-eligible patients in the BiRD phase II study, n=72 (68 evaluable); lenalidomide 25 mg for 21 of 28 days, dexamethasone 40 mg once a week, clarithromycin 500 mg twice a day continuously. There were 11 malignancies in 10 patients prior to enrollment. Rates of SPMs were retrospectively compared to background of all invasive cancers in the SEER database.	Overall response rate (ORR): 90%, CR/nCR: 53%; 2 year event-free survival (EFS) was over 97%. Median follow-up was over 5 years for efficacy and time to SPM. Median PFS was 70.8 months; median 5-year OS not reached. PFS is similar between patients going on to ASCT vs. lenalidomide maintenance. Median age was 75 years at time of diagnosis, so the expected incidence of SPM is 2.1 per 100 patient-years.	SPMs: no hematologic malignancies and 5 heterogeneous solid tumors, with 31.2 months median time from diagnosis. There were 6 cases noninvasive skin cancers, median time similar at 34 months from diagnosis. SPMs were not associated with specific myeloma chromosomal abnormalities, prior malignancy history, transplant status, gender, or lenalidomide maintenance. The SPM incidence rate of 2.85 is within the expected range.	Limitations: small cohort of patients, retrospective review, no bone marrow surveillance for MDS. Strengths: frontline study of lenalidomide, long follow-up, close monitoring of all patients, only data on patients with no alkylator priming. Conclusions: at 6 years of follow-up BiRD is highly effective in patients with newly diagnosed myeloma. There were no cases of MDS/AML. Frequency of SPMs was low and similar to incidence reported in SEER for age group. Some patients had invasive malignancies before diagnosis. All patients should have routine screening for SPMs.
Ruben Niesvizky, Weill Cornell Medical College, New York-Presbyterian Hospital, New York, New York, USA. (first author: Melitios Dimopoulos). Lenalidomide and dexamethasone (LEN plus DEX) treatment in relapsed/refractory multiple myeloma (RRMM) patients (pts) and risk of second primary malignancies (SPM): analysis of MM-009/010. Abstract 8009	Retrospective analysis of lenalidomide and dexamethasone (N=353) vs. placebo and dexamethasone (N=352) arms on MM009 and 010 trials in patients with relapsed, refractory myeloma comparing SPM incidence rates (IR) with SEER and other databases. Median follow-up for survival is 48 months.	Responses and safety have been previously published. Analysis limitations for this analysis include lack of AE reporting required during long- term follow-up after patients progress and discontinue from the study. Early stage SPMs may not be readily detected in patients with a progressive primary malignancy.	There were no cases of AML, and no B- cell malignancies. SPMs were heterogeneous and typical of an ageing population. During the active phase and follow-up period there were no statistically significant differences in incidence of invasive SPMs or in time to invasive SPM; 2 cases early after registration might have been preexisting. There were increased noninvasive skin cancers with lenalidomide vs. placebo. Most patients with invasive SPMs died of myeloma or other causes. There was a benefit for lenalidomide in TTP, OS, and OS after crossover vs. risk of SPM.	Conclusions: there was no difference in invasive SPMs for lenalidomide vs. placebo in these trials. SPM incidence rate is low and similar to background among similar age groups in the general population. OS is significantly longer for patients given lenalidomide and dexamethasone. Improvement in OS with lenalidomide is confirmed even with 50% crossover. The overall benefit-risk ratio for the use of lenalidomide remains strongly positive.
Brain Durie, Aptium Oncology, Inc., Cedars-Sinai Outpatient Cancer Center, Lost Angeles, California, USA. Long-term safety of lenalidomide (Len) in relapsed/refractory multiple myeloma patients (Pts): analysis of pooled data Abstract 8086	Pooled analysis of 11 Celgene-sponsored studies of lenalidomide in 3846 patients with relapsed/refractory myeloma (MM-007 to -010, MM-012, MM-016 to -019, MM-022; only MM-009 and MM-010 had control arms; most studies were of lenalidomide and dexamethasone; 007, 014, and 017 were lenalidomide monotherapy).	The incidence of SPMs in this patient population was compared with the expected background incidence of invasive cancers reported in the US SEER Cancer Registries for 2003 to 2007. 441 of the 3846 patients were older than age 75 years. 313 of these patients received lenalidomide-based therapy for 24 months or longer.	57 invasive SPMs were observed; 22 were in patients with 24 or more months of therapy. Incidence rates were similar independent of duration of treatment. 44 non-melanoma skin cancers were observed in 2729 person-years (1.61 per 100 person-years). The risk of death (24% at 5 years) is greater than the risk of SPMs (4% hematologic, 10% solid tumors at 5 years), and the 3-year OS is similar for patients with SPMs vs. the entire study population.	Lenalidomide-based therapy did not significantly increase the rate of SPMs compared with the incidence rate reported by SEER. The rate of SPMs was not significantly increased with increased duration of lenalidomide therapy. The benefit-risk profile of lenalidomide therapy for patients with relapsed, refractory myeloma is strongly positive.

development of SPMs is about 7% and the cumulative probability of death due to myeloma is over 90% as competing causes. So the risk of dying is a much larger problem than SPM on average. The median follow-up is 28 months for CALGB, with OS for lenalidomide at 90% and 83% for placebo, which was not seen in the other studies. The French study was closed, and the Italian study is ongoing; there is a PFS benefit in those two studies.

Summary and conclusions. Currently there is a lack of clear answers due to small numbers and study limitations. Benefits vs. risks must be considered. Even with lack of data, clinicians have to discuss facts with patients. The key question for the future is what are mechanisms of SPM development. There is a need to characterize molecular features of patients who develop SPM after myeloma, and there should be an effort to identify biomarkers.

Discussion. Dr. Palumbo believes that the risk of SPMs, particularly hematologic malignancies, is slightly increased with the use of lenalidomide, but that the risk of dying of myeloma that isn't treated with lenalidomide is much higher. Dr. Rossi thinks the risk is increased by the use of alkylating agents, and Dr. Niesvizky thinks that alkylators may contribute in the context of the order of agents used in therapy, i.e., induction with lenalidomide followed by alkylators, or the other way around, might be genotoxic. There is no information on the genetic profile of AML secondary to myeloma. Drs. Palumbo and Landgren are collecting data. Dr. Landgren said the NIH is collaborating with CALGB and the Italian group and is inviting everyone to work together because the number of cases is so low. If SPMs are included as events in the trials discussed, PFS does not change. There was a comment about how therapy could cause SPMs in such a short time period, given that most human carcinogens take longer to act. Dr. Landgren agrees latency needs to be taken into account. If AML is associated with treatment, it appears to occur about 4 years out, so longer follow-up is needed. The 3 studies presented that showed a small increase in SPMs in the treatment arm are suggestive but not definitive. Dr. Palumbo agrees about follow-up, and both he and Dr. Landgren point out the risk of SPM has to be compared with the much greater benefit derived from treatment. Dr. Campagnaro commented about the subset of patients in the BiRD study that presented with previous malignancies, noting that it was common to have patients with previous malignancies. She wondered if there is an enrichment for other prior tumors in patients who subsequently develop myeloma. Dr. Landgren responded that a study published in Leukemia this year reported prior tumors. However, because the average age of patients with myeloma is 71 years, this population can be expected to have other tumors. Men have a 50% chance and women a 30% chance of developing tumors over their life-span. There must be a study of different cancer types to see if those patients have a higher risk of developing myeloma. There are data suggesting other cancers are more likely to occur prior to myeloma, but the question needs further investigation. Dr. Lentzsch commented on the mechanism of induction of AML. Her group has studied the effect of IMiDs (lenalidomide and pomalidomide) on hematologic progenitors. PU1 is a transcription factor involved in differentiation that is down-regulated in patients treated with lenalidomide. An approach would be to look at PU1 in patients with AML and other malignancies. She also commented that it is important to provide a break in lenalidomide treatment to give cells a chance to differentiate. It could be important to look at the development of AML in patients given maintenance with continuous lenalidomide vs. those on a 3 weeks on, 1 week off schedule. Dr. Jakubowiak (session co-chair) asked the presenters if they would recommend maintenance with lenalidomide after transplant or non-transplant treatment outside of clinical trials. Dr. Palumbo said he would absolutely give lenalidomide after ASCT or conventional therapy but would monitor for the risk of SPMs with longer follow-up. Dr. Rossi said she would also definitely give lenalidomide maintenance because the risk of progression and death outweighs the risk of SPMs. Dr. Niesvizky proposed incorporating proteasome inhibition for maintenance in patients with high- risk disease. Dr. Landgren agreed, and stated that they need to be responsible and monitor the patients, and try to understand the mechanisms by which second malignancies develop.

New Therapies

Kenneth Anderson, Dana-Farber Cancer Institute, Boston, Massachusetts, presented **Bench-to-Bedside Translation of Targeted Therapies in Multiple Myeloma** as his David A. Karnofsky Memorial Award and Lecture. He reviewed the history of therapy and identification of cell lineages, and emphasized immune-based therapies, discussing monoclonal antibodies (mAbs) for cell depletion, targeted therapies, immunotoxins, and therapeutic vaccines. He also reviewed the role of the microenvironment in myeloma pathophysiology, and discussed new therapies being developed and tested in clinical trials, summarizing recently published

results. Some promising therapies or approaches include the following:

- Antibodies
  - ✓ Elotuzumab (anti-CS1 mAb). A phase III registration trial for new drug approval is testing lenalidomide plus dexamethasone with elotuzumab vs. lenalidomide plus dexamethasone. [See mAb presentation summaries below]
  - ✓ An anti-IL-17 antibody is in trial to reverse some immune deficits in patients with myeloma.
  - ✓ An anti-DKK1 mAb, BHQ880, abrogates the inhibitory effect of myeloma cells on osteoblastogenesis, and inhibits bone disease and myeloma cell growth in a mouse model.
  - ✓ BAFF is a member of the TNF family, and is expressed in membranous form by monocytes, dendritic cells, activated T cells, neutrophils, and stromal cells. Soluble BAFF serum levels in B-cell malignancies and myeloma are much higher than normal; 60% of patients with myeloma overexpress BAFF. An anti-BAFF mAb is being tested in combination with bortezomib. [See presentation summary below]
- Vaccines
  - ✓ A phase I trial of vaccination with dendritic cell-myeloma fusions in relapsed, refractory myeloma is underway.
- Proteasome inhibitors
  - ✓ Carfilzomib, an irreversible inhibitor of chymotryptic activity, is in ongoing phase III trials. [see presentation summaries below]
  - ✓ ONX 0912, an oral chymotryptic inhibitor, is in an ongoing phase I clinical trial in advanced solid tumors and has shown preclinical activity in myeloma.
  - ✓ MLN9708, an oral chymotryptic inhibitor, is in ongoing clinical trials.
  - ✓ NPI-0052 is in ongoing phase I/II trials.
- IMiDs
  - ✓ Pomalidomide is in phase I and phase II trials in relapsed, refractory myeloma. Dr. Anderson is "hopeful for accelerated approval because this agent will meet an unmet medical need."
- PI3/AKT/mTOR inhibitors
  - ✓ The AKT inhibitor perifosine and others have shown activity in combination with bortezomib and/or lenalidomide.
  - ✓ A phase III trial of bortezomib plus perifosine vs. bortezomib in relapsed myeloma is ongoing for FDA approval.
- Histone deacetylase (HDAC) inhibitors
  - ✓ Panobinostat to block the aggresome, plus bortezomib to inhibit the proteasome, has been shown to be active in a phase I/II trial in refractory myeloma.

Dr. Anderson observed that studying myeloma cells in the context of the bone marrow microenvironment as well as using genomics will help to define functionally important proteins to target on myeloma, further the understanding of myeloma pathogenesis, and identify appropriate patients for given therapies with the goal of developing personalized treatment.

Proteasome Inhibitors

Carfilzomib. The results of trials of carfilzomib are summarized in Table 4.

Jonathan Kaufman, Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia, USA, discussed the first 3 carfilzomib posters in the above table during the **Lymphoma and Plasma Cell Disorders Poster Discussion**. He made the following points:

- In PX-171-003, carfilzomib is effective as monotherapy in a heavily pretreated population of patients, is generally well tolerated with minimal treatment-emergent PN, and a subset of patients respond and can remain on therapy for a long period of time. It is not known what the optimal dose is in patients with refractory disease.
- In PX-171-004, carfilzomib is effective as a single agent in bortezomib-naïve patients. It is not known if there is a dose-response effect or if higher doses should be used. There are no studies asking if there is a PFS or OS advantage vs. best standard care. It is not known how the safety, including the low rate of PN, and the efficacy would compare with what Dr. Kaufman referred to as the "optimal" bortezomib schedule of once-weekly I.V. or subcutaneous administration.
- In PX-171-006, in combination with lenalidomide, no dose-limiting toxicities (DLT) were observed, and AEs were as expected. The combination CRd is very effective in patients with relapsed myeloma and can be administered

Table 4.

Presenter Title Abstract	Study Patients Follow-up	Dose and schedule	Results	Conclusions
Michael Wang, MD Anderson Cancer Center, Houston, Texas, USA Interim results from PX-171-006, a phase 2 multicenter dose-expansion study of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed and/or refractory multiple myeloma. Abstract 8025 (poster)	PX-171-006, phase II. Relapsed, refractory myeloma after 1 to 3 prior therapies, N=52 (cohort 6 and expansion group of a dose finding study).	MPD (maximum protocol-specified dose) = phase II recommended dose: 20/27 mg/m^2 carfilzomib (20 cycle 1, day 1 and 2, then 27 thereafter); 40 mg dexamethasone weekly; lenalidomide 25 mg/day [CRd].	ORR 78% (of 40 response-evaluable patients); 41% ≥VGPR. Most common grade 3 to 4 AE: neutropenia, anemia, thrombocytopenia, hypophosphatemia; hematologic AEs reversible and manageable 9.6% drug-related SAE: hypoxia, GI hemorrhage, facial edema, pneumonia.	Ongoing for PFS, DOR (duration of response). ASPIRE, ongoing phase III open-label trial is comparing CRd to Rd and is actively recruiting (see Moreau poster summary below).
Keith Stewart, Mayo Clinic, Scottsdale, Arizona, USA Carfilzomib produces a high single-agent response rate in patients with bortezomib-naïve relapsed multiple myeloma: updated interim results from the PX-171-004 study. Abstract 8026 (poster)	PX-171-004, phase II non-randomized, open-label, single-arm. Relapsed or relapsed/refractory myeloma after 1 to 3 prior regimens excluding bortezomib Cohort 1 N=59, median follow-up 17.5 months, Cohort 2 N=70, median follow-up 10.3 months.	Carfilzomib single-agent. Cohort 1: 20 mg/m^2 days 1, 2, 8, 9, 15, 16 every 28 days up to 12 cycles Cohort 2: same as cohort 1 for first cycle, then 27 mg/m^2 for subsequent cycles; dexamethasone 4 mg given to all patients first cycle, first dose escalation cycle cohort 2, and if treatment-related infusion reactions occurred.	ORR cohort 1 and 2: 42% and 51%. Cohort 1: median TTP 8.3 months, median DOR 13.1 months. Cohort 2: median TTP 10.3 months, median DOR not reached AE similar between cohorts 1 and 3: PN grade 1-2 14% and 17%, PN all grades 15% and 17%; grade 3 AE >5% in either cohort: fatigue, anemia, lymphopenia, thrombocytopenia, neutropenia, pneumonia.	Recommended phase III dose is 20/27 mg/m^2 Study is ongoing; 22 patients are receiving carfilzomib on extension trial PX-171-010. 3-year long-term follow-up OS, DOR, TTP, and safety will be reported when available.
David Siegel, John Theurer Cancer center, Hackensack, New Jersey, USA. PX-171-003-A1, an open-label, single-arm phase 2 study of carfilzomib in patients with relapsed and refractory multiple myeloma: long-term follow-up and subgroup analysis. Abstract 8027 (poster)	PX-171-003-A1, phase II open-label, single-arm. Relapsed and refractory myeloma after ≥2 lines of therapy including bortezomib or an IMiD; N=266. Median follow-up 14. 3 months.	20/27 mg/m^2 carfilzomib (20 cycle 1, day 1 and 2, then 27 thereafter).	N=257 evaluable for response: ORR 24%, ORR + MR (CBR) 37%. DOR for ORR: 7.8 months; DOR for CBR population: 8.3 months ORR lower for patients with ISS stage III disease or bortezomib-refractory disease median OS 15.6 months; median PFS 3.7 months. Grade 3-4 AEs primarily hematologic; new onset or grade 3-4 PN rare.	27 patients continuing on extension protocol PX-171-010 ORR and CBR rates are final; OS data will be updated.
Jackie Szymonifka, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA. Phase II study of carfilzomib (CFZ) in combination with current agents for relapsed and refractory multiple myeloma (RRMM). Abstract 8028 (poster)	Phase II Relapsed, refractory myeloma, N=74.	20/27 mg/m^2 carfilzomib (20 cycle 1, day 1 and 2, then 27 for rest of cycle 1); cycle 2 onwards: could be escalated to 36, 46, 54 mg/m^2 additional agents added at cycle 2 in various combinations included vorinostat, thalidomide, doxorubicin, tocilizumab, lenalidomide, cyclophosphamide, bevacizumab, cisplatin, rapamycin.	nCR/CR: 18%; PR: 19%; improvement in 54%. 6-month estimates OS: 54%; EFS 21%. Toxicities related to number of cycles and additional drugs added to carfilzomib.	EFS benefit seen in GEP-defined low- risk myeloma. Carfilzomib has activity, especially in combination with other agents in this population of patients with advanced disease.

Table 4. *(continued)*

Presenter Title Abstract	Study Patients Follow-up	Dose and schedule	Results	Conclusions
Philippe Moreau, University Hospital, Nantes, France. A randomized, multicenter, phase 3 study comparing carfilzomib, lenalidomide, and dexamethasone to lenalidomide and dexamethasone in patients with relapsed multiple myeloma. Abstract TPS225 (poster)	ASPIRE Phase III, randomized, open-label in relapsed myeloma (1 to 3 prior regimens). Accrual goal N=700.	Rd vs. CRd 28-day cycles. carfilzomib arm: 20/27 mg/m^2 carfilzomib (20 cycle 1, day 1 and 2, then 27 for rest of cycle 1 and subsequent cycles) both arms: lenalidomide 25 mg days 1 to 21 dexamethasone 40 mg days 1, 8, 15, 22.	149 patients enrolled as of end of April 2011 at 91 centers.	Treatment will continue until disease progression or unacceptable toxicity. Primary endpoint is PFS, secondary endpoints include OS, ORR, DOR, safety.

for prolonged periods of time. However, it is not known if CRd has an advantage over Rd. The ASPIRE ongoing phase III trial will test this.

Monoclonal Antibodies (mAbs)

Development of monoclonal antibodies (mAbs) as therapeutics for myeloma continues. mAbs in development include:

- LY2127399, a human IgG4 anti-BAFF neutralizing antibody.
- Lorvotuzumab mertansine, an antibody-drug conjugate targeting CD56 (a neural cell adhesion molecule, NCAM1, expressed on about 70% of myeloma cells but not normal plasma cells); the antibody delivers the cytotoxic maytansinoid DM1 to cells where it inhibits tubulin polymerization when cleaved after internalization.
- Elotuzumab, a humanized monoclonal IgG1 antibody targeting human CS1, a cell surface glycoprotein expressed on myeloma cells.

Presentations on mAbs are summarized in Table 5.

Discussion. Abstracts 8012 to 8014 were discussed by Nikhil Munshi, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, who was filling in for Asher Alban Chanan-Khan. He observed that investigators are still looking for the "rituximab" for myeloma. To this end, there are over 10 potential mAb candidates that have entered clinical development. The anti-tumor activity of mAbs as single agents has been modest to date, so combination approaches with immunomodulatory and other drugs are therefore required.

Issues to be addressed in the future for the anti-BAFF mAb include confirmation of efficacy and synergism in larger studies, determination of the response in patients with bortezomib-refractory disease, and identification of biomarkers for patient selection and response prediction. The effects on bone disease may also be interesting.

For lorvotuzumab mertansine, the study was restricted to patients with CD56- positive myeloma, which allows identification of patients who may respond. It is encouraging that the associated PN is reversible. For the future, we need a larger study with LM to confirm its efficacy and synergy with other drugs, the response in lenalidomide-refractory myeloma, and the dose and schedule to prevent PN.

The strength of the elotuzumab study is that it involves a large number of patients, and therefore is probably reproducible. Randomized trials are underway to confirm the efficacy of elotuzumab in combination with lenalidomide. It would be interesting to see if elotuzumab has single-agent activity in SMM, and if there is a biomarker useful to predict response such as the CS1 expression level or basal NK cell number.

Histone Deacetylase (HDAC) Inhibitors

PANORAMA 1: a multicenter, randomized, double-blind, placebo-controlled phase 3 study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma (Abstract TPS227) was presented by Jesus San-Miguel, University Hospital of Salamanca, Salamanca, Spain, in the Trials in Progress Poster Session. This trial will enroll 672 patients who have received 1 to 3 prior lines of therapy and whose myeloma is not bortezomib-refractory. They will be randomly assigned to bortezomib and dexamethasone with either panobinostat or placebo for eight 21-day cycles (standard bortezomib); those who have clinical benefit can continue on therapy for an additional four 42-day cycles (weekly bortezomib). The primary endpoint is PFS, and final analysis will be performed when a total of 460 PFS events have been observed. The study will also collect information on biomarkers and quality of life. As of May, 2011, 400 patients had been randomly assigned to treatment.

Table 5.

Presenter Title Abstract	Study Patients	Dose and schedule	Results	Conclusions
Noopur S. Raje, Massachusetts General Hospital, Boston, Massachusetts, USA. Phase I study of LY2127399, a human anti-BAFF antibody, and bortezomib in patients with previously treated multiple myeloma. Abstract 8012	Phase I, non-randomized, uncontrolled, open-label study of LY2127399 in combination with bortezomib to determine the recommended phase II dose. Patients (N=20) with relapsed or refractory myeloma with at lease 1 prior regimen; patients with light chain disease included.	5 dose levels LY2127399: 1, 10, 30, 100, and 300 mg with a 100 mg cohort expansion based on PK data cycle 1. Conventional bortezomib regimen. LY2127399 on day 1 of cycles; no dexamethasone allowed.	9 patients had grade 3 and 4 AE: thrombocytopenia associated with bortezomib, neuropathy, neutropenia; hypercalcemia, and hyperuricemia in PD. LY2127399 was well tolerated: no infusion-related reactions, no premedication or steroids, 5 SAE. Pancreatitis in 1 patient (not seen previously with LY2127399 or bortezomib). Are seeing responses PR or better in about half of patients. TTP is 4.9 months, DOR is 9.7 months in responders.	100 mg dose of LY2127399 selected for cohort expansion. AEs similar to those expected with bortezomib alone. They are encouraged to move to randomized studies of LY2127399 plus bortezomib vs. bortezomib. LY2127399 is also in phase III trials for rheumatoid arthritis and systemic lupus erythematosus.
Jesus G. Berdeja. Sarah Cannon Research Institute, Nashville, Tennessee, USA. Phase I study of lorvotuzumab mertansine (LM, IMGN901) in combination with lenalidomide (Len) and dexamethasone (Dex) in patients with CD-56-positive relapsed or relapsed/ refractory multiple myeloma (MM). Abstract 8013	Phase I dose escalation study in CD56-positive myeloma to determine maximum tolerated dose (MTD) of lorvotuzumab mertansine plus lenalidomide and dexamethasone. Patients (N=16) with relapsed or relapsed/ refractory, CD56- positive myeloma with at least 1 prior therapy; prior lenalidomide was allowed.	28 day cycles of, standard lenalidomide, dexamethasone 40 mg weekly, days 1, 8, 15. I.V. lorvotuzumab mertansine dose escalation with 3 dose levels: 75, 90, 112 mg/m^2	13 patients were evaluable for response: ORR = 61.5%. Dose reduction was necessary in most patients for PN at the 2 higher doses, but most continued to respond and PN improved. Most grade 3 events were PN, with no grade 4 or 5 AE and no cycle 1 DLTs.	The 75 mg/m^2 lorvotuzumab mertansine dose level was expanded and is enrolling with no dose reduction at this level.
Philippe Moreau, University Hospital, Nantes, France, presented for Paul Richardson. Elotuzumab with lenalidomide and low-dose dexamethasone in patients with relapsed multiple myeloma: a randomized phase II study. Abstract 8014	Phase I/II study design. N=98 The main objectives of the study were to determine the MTD of elotuzumab plus lenalidomide plus low dexamethasone in phase I, and efficacy in relapsed, refractory myeloma in phase II. Secondary objectives included PFS and determining the efficacy of a premedication regimen for minimizing infusion-related reactions in late phase I and in phase II. Prior lenalidomide was allowed in phase I but not phase II.	Standard lenalidomide 21 of 28 days; 40 mg dexamethasone. Elotuzumab cycles 1 and 2 once a week; cycles 3 onward, twice a month. Phase I elotuzumab up to 20 mg/kg; Phase II patients randomly assigned to 10 or 20 mg/kg elotuzumab. Premedication regimen: methylprednisolone (later replaced with dexamethasone), diphenhydramine or equivalent, ranitidine or equivalent, acetaminophen.	ORR: 82%; CR: 9%; ≥VGPR: 32%. ORR 10 mg: 92%; ORR 20 mg: 75%. ORR was 90% if 1 prior therapy, ORR was 76% if at least 2 prior therapies. Median TTR: 1 month; median time to best response = 1.9 months. At a median follow-up of 9.4 months the median PFS was not reached. The 2-year projected PFS = 70%. Most treatment- emergent grade 3 and 4 AEs were related to lenalidomide (anemia, neutropenia, thrombocytopenia, lymphopenia). Elotuzumab-related AE were mostly infusion reactions; 56% had nausea or headache or other symptoms. CS1 saturated almost 100% of CD38 binding sites in bone marrow myeloma cells at either dose.	10 mg/kg is the recommended phase III dose because there was no difference in response rates between 10 mg vs. 20 mg and 10 mg can saturate 100% of CS1 at the cell surface with good response. The ORR of 90% in patients only 1 prior therapy provides the rationale for using this combination earlier in disease. Two phase III trials are being conducted in relapsed myeloma and as frontline therapy.

Table 5. *(continued)*

Presenter Title Abstract	Study Patients	Dose and schedule	Results	Conclusions
Sagar Lonial, Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia, USA. Phase I trial of elotuzumab, lenalidomide, and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma. Abstract 8076 (poster)	Phase I data from a phase I/II trial to assess MTD, safety, and efficacy. Patients with relapsed/refractory myeloma (N=28 treated; 23 evaluable for response). Median follow-up 16.4 months.	3 cohorts with dose escalation of elotuzumab (5, 10, and 20 mg/kg days 1, 8, 15, and 22 of the first 2 cycles and days 1 and 15 of subsequent cycles) plus 25 mg lenalidomide days 1 to 21 and 40 mg dexamethasone weekly, 28-day cycle. Protocol amended for premedication for infusion reactions.	No DLTs, MTD not reached. Most common AEs included fatigue, diarrhea, anemia, nausea, constipation, and neutropenia; most common grade 3 and 4 AEs were neutropenia and thrombocytopenia. Infusion reactions were not dose-related and were mitigated with premedication. ORR: 82%; median TTR 1.6 months; median PFS not reached.	Adequate CS1 receptor saturation occurred at both 10 and 20 mg/kg doses. A phase II trial of elotuzumab in combination with lenalidomide and dexamethasone is ongoing.

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