REVIEW

Challenges in multiple myeloma diagnosis and treatment

S Girnius^{1,2} and NC Munshi^{1,3,4}

Although multiple myeloma (MM) remains an incurable disease, the advent of novel treatment paradigms has improved survival outcomes in the past two decades. This includes widespread use of high-dose chemotherapy with autologous stem cell transplantation (HDT–ASCT) and the development of the novel agents thalidomide, lenalidomide and bortezomib. The efficacy and tolerability of these novel agents have allowed for the exploration of continuous therapy approaches. Maintenance therapy after HDT–ASCT, for example, may help prolong progression-free survival by providing sustained control of residual disease. Trials are also under way to evaluate lenalidomide in patients with high-risk smoldering MM, with the aim of delaying progression to symptomatic MM. Other research is focusing on improving HDT–ASCT protocols and integrating novel agents, such as bortezomib, as an induction or consolidation therapy. Despite these advances, more effective strategies are needed, particularly for the management of older, less fit patients who are ineligible for HDT–ASCT. Preliminary results on the use of lenalidomide maintenance therapy in elderly patients are encouraging. Taken together, these observations indicate that in this era of novel agents, optimal treatment of MM requires a long-term perspective that focuses on providing sustained disease control while maintaining quality of life.

Leukemia Supplements (2013) 2, S3–S9; doi:10.1038/leusup.2013.2

Keywords: multiple myeloma; challenges; novel agents; elderly

INTRODUCTION

Multiple myeloma (MM) is an incurable plasma cell neoplasm accounting for 1% of all malignancies and 10% of hematologic malignancies.^{1,2} In 2011, the estimated annual incidence of new cases of MM was 20 520.³ The incidence is 5.7 per 100 000 population, with rates almost twice as high among African Americans.³ MM affects a higher proportion of elderly patients with an age-adjusted incidence rate of 30.3 per 100 000 population aged >65 years. The median age at diagnosis is 70 years, and with the aging US demographic, the overall incidence of MM is expected to rise.

The advent of novel treatment paradigms has improved survival over the past two decades. The first major therapeutic milestones were autologous stem cell transplantation (ASCT) in the 1980s and the introduction of novel agents, such as thalidomide in 1999, and bortezomib and lenalidomide in 2003 and 2005, respectively. The Surveillance, Epidemiology and End Results (SEER) database showed a modest increase in 5-year relative survival rates from 1975 to 2000 (from 25 to 32%).³ However, from 2001 to 2007, the 5-year relative survival rate increased to 41.1%; this benefit was seen primarily in younger patients.⁴ Life expectancy in younger patients with standard-risk MM is now 7–10 years.⁵ In patients aged >70 years, there was no statistically significant difference in 5- or 10-year estimates of overall survival (OS) from 1990 and 2002. However, a trend towards improved 5-year survival in patients aged 60–69 years has been observed ($P=0.09$).⁴ Median survival in patients with newly diagnosed MM (NDMM) improved from 29.9 months in those diagnosed between 1971 and 1996 to 44.8 months for those diagnosed in the following decade ($P<0.001$).⁶ These studies followed cohorts until the mid 2000s; hence, the effects of novel agents had not yet been maximized. In this review, we will discuss the use of novel agents in the treatment of MM and long-term strategies to provide sustained disease control, maintain good quality of life and optimize outcomes.

DIAGNOSIS

MM is typically detected on routine blood work, or by characteristic symptoms caused by infiltration of myeloma cells or end-organ damage related to effects of secreted and/or deposited immunoglobulins. Patients can present with bone pain—often precipitated by movement (58%)—fatigue (32%) or weight loss (24%).⁷ Fatigue correlates with anemia (median hemoglobin of 9.9 g/dl). The majority of patients with MM have a localized band on a serum protein electrophoresis, a monoclonal protein detected by immunofixation or abnormal light chains in the urine or serum.

Plasma cell dyscrasia encompasses a spectrum of disorders, from monoclonal gammopathy of unknown significance (MGUS) to smoldering MM, to symptomatic MM. The International Myeloma Working Group Consensus Panel provided diagnostic criteria for plasma cell disorders.⁸ Differentiation among MGUS, smoldering MM and symptomatic MM is based on the level of serum monoclonal protein, the percentage of clonal plasma cells in bone marrow and the presence or absence of end-organ damage, such as hypercalcemia, renal insufficiency, anemia or bone lesions. In addition, consideration and evaluation for amyloid light-chain amyloidosis or light-chain deposition disease is recommended, especially in patients fitting the criteria for MGUS.⁹

STAGING AND RISK STRATIFICATION

Significant heterogeneity in the natural history and response to treatment has been observed in MM. Even in 2007, 24% of NDMM patients died within 1 year of diagnosis, whereas a small percentage of patients will live for longer than a decade now.³ Several prognostic factors have been established to identify patients with high-risk disease. The International Staging System (ISS) classifies patients with MM into one of three stages based on serum β_2 -microglobulin and albumin levels: stage I is

¹Boston VA Healthcare System, Boston, MA, USA; ²Boston University Medical Center, Boston, MA, USA; ³Dana Farber Cancer Institute, Boston, MA, USA and ⁴Harvard Medical School, Boston, MA, USA. Correspondence: Dr NC Munshi, Dana Farber Cancer Institute, 44 Binney Street, M1B28, Boston, MA 02115, USA. E-mail: Nikhil_Munshi@dfci.harvard.edu

characterized by serum β_2 -microglobulin <3.5 mg/l and serum albumin >3.5 g/dl; stage II patients do not meet the criteria for stage I or III; and stage III is characterized by serum β_2 -microglobulin ≥ 5.5 mg/l.¹⁰ In the era before the approval of bortezomib and lenalidomide, median survival for stages I, II and III MM disease were 62, 44 and 29 months, respectively. The ISS was validated and found to be significant irrespective of age, conventional versus high-dose treatment and geographical location. Although platelet count had a higher hazard ratio (HR) than serum albumin, it occurred less frequently and was not incorporated into the ISS. Elevated serum lactate dehydrogenase also correlated with high tumor mass, decreased response rate and shorter median survival.¹¹

Cytogenetic abnormalities

Detection of certain cytogenetic abnormalities carries a poor prognosis, but standard karyotyping is hindered by the low proliferative index of myeloma cells and the difficulty in aspirating malignant clones.¹² More recently, fluorescence *in situ* hybridization has been incorporated into standard workup, as it can detect chromosomal abnormalities in non-mitotic cells. In particular, the del(17p) and t(4;14) abnormalities are associated with shorter event-free survival (EFS; HR 3.29 and 2.79, respectively) and OS (HR 3.93 and 2.78, respectively).¹² The presence of these two cytogenetic abnormalities predicts significantly worse EFS and OS ($P \leq 0.001$) across all three ISS stages. In patients with a low β_2 -microglobulin level and without del(17p) and t(4;14), the expected 4-year survival rate is 83%. In comparison, median OS in patients with either a cytogenetic abnormality or an elevated β_2 -microglobulin level is 19 months. Another cytogenetic abnormality linked with worse outcome is t(14;16).¹³ Del(13) also has a high incidence in MM and a negative impact on EFS and OS, but its effect is not significant in the absence of del(17p) and/or t(4;14).¹² Overall, the consensus recommendation is to perform cytogenetics and fluorescence *in situ* hybridization for the 17p13, t(4;14) and t(14;16) abnormalities. However, the optimal treatment approach for patients with high-risk MM based on the presence of ≥ 1 cytogenetic abnormality has not been established as prospective, randomized studies are lacking. In one study, 100 consecutive patients, of which 16% had high-risk cytogenetics, received lenalidomide plus dexamethasone.¹⁴ At a median follow-up of 36 months, the group with high-risk cytogenetics had worse progression-free survival (PFS; 18.5 versus 36.5 months; $P < 0.001$), but similar response rates ($P = 0.36$) and OS as those with a standard-risk cytogenetic profile ($P = 0.4$); the median OS was not reached in either arm. Half of the high-risk patients who relapsed received bortezomib as a salvage therapy. Longer follow-up and a larger series are necessary to determine whether novel agents may overcome high-risk cytogenetic features in MM.¹⁵

Serum free light-chain assay

Importantly, measurement of serum free light chains (FLCs) has become integral to screening for plasma cell dyscrasia, risk stratification of patients with MGUS and smoldering MM, disease staging and response assessment. The serum FLC immunoassays have a very low limit of detection (< 1 mg/l) compared with serum protein electrophoresis (1–2 g/l) or immunofixation electrophoresis (150–500 mg/l).¹⁶ The sensitivity and specificity of serum FLCs alone are 0.76 and 0.96, respectively.¹⁷ However, the addition of serum FLCs to serum immunofixation electrophoresis and serum protein electrophoresis improved the sensitivity for detecting paraproteinemia to 99.5%.¹⁸ Serum FLCs are still insufficient in certain cases of MM with light-chain excretion in the urine and in detecting amyloid light-chain amyloidosis; thus, a 24-hour urine immunofixation electrophoresis is necessary in the initial workup and when considering amyloid light-chain amyloidosis.¹⁶

Serum FLCs have been incorporated into models predicting progression of MGUS or smoldering MM to symptomatic MM, or related disorders such as amyloid light-chain amyloidosis or light-chain deposition disease. In a single-institution retrospective study, multivariate analysis showed that an abnormal serum FLC ratio increased the risk of progression from MGUS to MM by an HR of 2.6 ($P < 0.001$).¹⁹ This study concluded that three risk factors could predict progression from MGUS to MM or a related disorder: (a) an abnormal serum FLC ratio; (b) a serum monoclonal protein level > 15 g/l; and (c) non-immunoglobulin G subtype. The same group investigated prognostic factors for progression of smoldering MM. Multivariate analysis showed that an abnormal FLC ratio of < 0.125 or > 8 increased the risk of progression by an HR of 1.9 ($P < 0.01$).²⁰

The use of serum FLCs for staging has been proposed. Van Rhee *et al.*²¹ have reported that patients with FLCs > 75 mg/dl had more aggressive disease features with more renal failure, higher percentages of bone marrow plasma cells, higher values of β_2 -microglobulin and lactate dehydrogenase, higher proportion of light-chain disease and higher proportion of ISS stage III disease, all of which correlate with worse OS and EFS.²¹ In fact, Snozek *et al.*²² have reported improved prognostic capacity of ISS, with inclusion of FLCs in the staging system, especially in patients with stage II disease.²² The most recent International Myeloma Working Group Consensus Panel recommendations did not incorporate serum FLC in staging.²³

MANAGEMENT

Smoldering MM

Smoldering MM presents with a higher burden of disease than MGUS and has a higher rate of progression to MM or related diseases. The risk of progression is 10% annually for the first 5 years, or 51% at 5 years.²⁴ The rate of progression decreases to 3% annually for the next 5 years, and the 15-year risk is 73%. A multivariate analysis showed three risk factors for progression: (a) bone marrow plasma cells $\geq 10\%$; (b) a serum monoclonal protein level ≥ 3 g/dl; and (c) a serum FLC ratio of < 0.125 or > 8 . The 5-year rate of progression was 15, 43 and 69%, and the median time-to-progression was 19, 8 and 2 years, for patients with one, two and three risk factors, respectively. Flow cytometry assessment of the bone marrow aspirate to stratify progression has been proposed.²⁵ Immunoparesis and $> 95\%$ of clonal or abnormal plasma cells on flow cytometry have also been identified as risk factors. With this method, the 5-year progression rate was 4, 46 and 72% for patients with no, one and two risk factors, respectively. Another risk factor for early progression of asymptomatic MM is occult bone disease detectable by magnetic resonance imaging.²⁶

Several clinical trials are investigating the role of preventative chemotherapy to delay the onset of symptomatic MM. A study of asymptomatic stage I MM treated with early or deferred melphalan plus prednisone (MP) in the mid 1980s did not show a difference in response rate, duration of response or OS.²⁷ A randomized controlled study showed that zoledronic acid decreased skeletal-related events, but did not change time-to-progression.²⁸ Those studies preceded newer agents and improved risk stratification. More recently, several studies have looked at lenalidomide in high-risk smoldering MM. In an ongoing phase III, randomized multicenter trial conducted by Mateos *et al.*,²⁹ 118 patients with high-risk smoldering MM received nine 4-week cycles of induction lenalidomide plus dexamethasone treatment, followed by maintenance lenalidomide therapy or observation. The overall response rate was 75% in the intent-to-treat population and 91% in those who completed induction. With a 16 month follow-up, 23% (13/57) of patients receiving lenalidomide plus dexamethasone progressed to active MM

compared with 34% (21/61) in the observation arm. The estimated HR was 6.7 (95% confidence interval 2.3–19.9). The median time-to-progression in the lenalidomide plus dexamethasone arm was not reached compared with 25 months in the observation arm ($P < 0.0001$); there was no statistically significant difference in mortality. In the United States, an ongoing Eastern Cooperative Oncology Group trial (ClinicalTrials.gov: NCT01169337) is comparing six cycles of lenalidomide to observation in patients with high-risk smoldering MM, but preliminary results are not yet available. Despite identification of a subset of smoldering MM patients with a high-risk of progression, the data for preventive chemotherapy are promising but have not matured sufficiently.

Symptomatic MM—goals of therapy

More aggressive treatment of NDMM with combination novel agents has increased complete response (CR) rates and PFS, although its long-term impact on improvement in OS remains to be confirmed.³⁰ The debate regarding the best treatment objectives (cure versus control) continues.³¹ Supporters of the curative approach believe that MM is more sensitive to therapy early in the disease course, and thus recommend aggressive therapy at diagnosis. Alternatively, those espousing the control approach prefer sequential therapy that minimizes adverse events and improves quality of life, as cure is unlikely. Use of aggressive combination approaches, such as stem cell transplantation in the 'Total Therapy' program, has led to long-term sustainment of CR indicative of a possible cure in a fraction of patients with MM.

Transplantation-eligible patients

The standard of care for patients aged <65 years with NDMM, with no comorbidity, includes high-dose chemotherapy followed by ASCT. Several studies have compared conventional chemotherapy with ASCT;³² two of these showed improvement in OS with ASCT.^{33,34} A meta-analysis of nine studies with a total of 2411 patients showed that ASCT improved PFS, but did not show an OS benefit.³⁵ The improvement seen in PFS was also applicable in chemorefractory disease. In high-risk disease, the median OS is 2–3 years, compared with 5 years in standard-risk myeloma.⁹ More recently, use of novel agents before ASCT (induction) or after ASCT (maintenance), tandem transplantations and allogeneic stem cell transplantation are being reinvestigated to improve survival.

Induction therapy. The goal of induction therapy is to achieve a minimal disease status that allows for successful use of ASCT. It also reduces plasma viscosity and provides symptom control.⁹ Compared with a historical combination, such as vincristine, doxorubicin and dexamethasone, which produces response rates of 40–70%,⁹ novel agents can achieve impressive response rates. As CR after induction therapy correlates with CR after ASCT, novel agents have been examined for induction chemotherapy.³⁶

Thalidomide was the first novel agent used as an induction therapy. Regimens such as thalidomide and dexamethasone, and thalidomide, doxorubicin and dexamethasone have been evaluated.^{37–39} Lenalidomide, a second-generation immunomodulator with a different toxicity profile to thalidomide, has also been evaluated in patients with NDMM.⁴⁰ In a randomized trial, the combination of lenalidomide and low-dose dexamethasone produced superior survival outcomes compared with lenalidomide and standard-dose dexamethasone.⁴¹ A short induction course of lenalidomide plus standard-dose dexamethasone does not hamper stem cell collection, with 91% of patients obtaining a sufficient yield with one or two collections.⁴² With a novel and different mechanism of action, bortezomib has also been explored as an induction therapy. In a phase III, multicenter European study that randomized 482 patients to induction chemotherapy with

vincristine, doxorubicin and dexamethasone, or bortezomib plus dexamethasone (VD), the VD cohort had a better CR rate (5.8% versus 1.4%; $P = 0.012$), CR plus very good partial response rate (37.7% versus 15.1%; $P < 0.001$) and overall response rate (78.5 versus 62.8%; $P < 0.001$).⁴³ Survival data in this study are difficult to interpret since 88% of patients were then enrolled in a lenalidomide consolidation study. Nonetheless, there was a trend towards improved PFS in the VD group (36.0 versus 29.7 months; $P = 0.064$).

Multidrug approaches, especially bortezomib-based, for induction chemotherapy are being explored. The combination of lenalidomide, bortezomib and dexamethasone (RVD) has produced an overall response rate of 100%, including 74% of patients achieving a very good partial response or better, making this combination a standard of care in NDMM.⁴⁴ The 18-month PFS and OS were 75% and 97%, respectively. The multicenter, phase I EVOLUTION (Evaluation of Velcade, dexamethasone and Lenalidomide with or without cyclophosphamide Using Targeted Innovative ONcology strategies in the treatment of frontline MM) study evaluated the safety and efficacy of combination cyclophosphamide, lenalidomide, bortezomib and dexamethasone, and reported results that were not significantly superior to the RVD regimen.⁴⁵ Other induction regimens, such as bortezomib, cyclophosphamide and dexamethasone, and bortezomib, thalidomide and dexamethasone have also been assessed.^{46,47}

It should be noted that a post-transplantation CR correlates with prolonged PFS and OS, especially if sensitive CR criteria, such as molecular remission or multiparameter flow cytometry, are used.³² However, the data on thalidomide predated serum FLC; hence, one must be cautious concluding that an improved response rate will result in improved survival. The data on bortezomib and lenalidomide included serum FLC, but reported primarily response rates to induction chemotherapy. Further refinement of CR assessment using newer technologies is needed, and assessment of the impact of CR on survival outcomes is warranted.

Allogeneic stem cell transplantation. Because of graft-versus-myeloma effect, allogeneic stem cell transplantation is currently the only curative therapy for MM. The prospect of curative treatment is seductive, but the treatment-related mortality from myeloablative conditioning in a heavily pretreated patient is 41%.⁵ Because of this high treatment-related mortality, survival in allogeneic stem cell transplantation is inferior to ASCT. Reduced-intensity conditioning with allogeneic stem cell transplantation is associated with lower treatment-related mortality and has, therefore, been compared with tandem ASCT. Several multicenter trials conducted in Europe and the United States, however, have failed to show a survival benefit with reduced-intensity conditioning with allogeneic stem cell transplantation and, in fact, showed a trend towards improved PFS with tandem ASCT.⁵

Maintenance therapy. Novel agents have been used as maintenance therapy after ASCT. Several previous studies have evaluated the role of maintenance therapy in MM using interferon, steroids, thalidomide, lenalidomide and bortezomib. Two studies have recently evaluated lenalidomide maintenance therapy after ASCT^{48,49} and both the studies demonstrated a significant improvement in PFS, and one found an improvement in OS with lenalidomide maintenance compared with placebo.⁴⁹ However, the incidence of the second primary malignancy was reported to be increased in the group receiving lenalidomide maintenance compared with placebo. Nevertheless, currently, the significant benefit observed with lenalidomide maintenance suggests that continued use of lenalidomide maintenance may be warranted after careful discussion with patients. These trials are ongoing and continue to collect OS information.

Transplantation-ineligible patients

Historically, the MP regimen was the standard of care in patients who were not transplantation candidates. Frontline therapies are evolving, as multiple new agents and combinations are explored. In a meta-analysis, thalidomide-based regimens such as MP plus thalidomide showed superior efficacy to MP, but increased the risk of adverse events.^{50,51}

Lenalidomide-based regimens have also been evaluated in transplantation-ineligible patients. These regimens include lenalidomide plus dexamethasone,^{52,53} MP plus lenalidomide (MPR), with or without single-agent lenalidomide maintenance,^{52,54} and the BiRD (clarithromycin, lenalidomide and dexamethasone) regimen.^{53,55}

Lastly, bortezomib was found to prolong PFS and OS when combined with MP in the phase III VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone) trial.⁵⁶ Total grade 3 or 4 adverse event rates were similar across both the MP group and the bortezomib plus MP group, and the peripheral neuropathy associated with bortezomib was reversible. Longer follow-up confirmed improved survival (HR 0.653; $P < 0.001$).⁵⁷ In summary, novel agents have been incorporated into the management of patients with NDMM, including transplantation-eligible and -ineligible patients. Although this has improved response rates and PFS, it remains to be seen how this will affect OS. We believe that a bortezomib-based regimen is the standard of care because of the associated rapid response, improved response rate, prolonged survival and excellent response to other agents after relapse. However, the optimal sequence of chemotherapies remains to be determined.

Elderly patients. Although significant progress has been made in the management of MM, the benefit has been seen primarily in younger patients. With an average age of diagnosis at 70 years, most MM patients are elderly, which generates several challenges (Table 1). Many patients have comorbidities that frequently preclude aggressive therapies, such as ASCT. Reduced-intensity ASCT can be offered in younger patients, which is associated with a longer EFS (28 versus 15.6 months; $P < 0.0001$) and OS (not reached at 41 months follow-up versus 42.5 months; $P < 0.0005$) when compared with MP. ASCT was associated with higher early mortality, greater transfusion requirements and fevers of unknown origin.⁵⁸

In patients who are ineligible for ASCT, standard treatment typically includes the MP regimen, combined with either thalidomide or bortezomib, or lenalidomide and low-dose dexamethasone.⁵⁹ It is important to remember that all the options

available to younger transplantation-eligible patients are also available and effective in older patients. This includes bortezomib plus dexamethasone and three-drug combinations, such as bortezomib, cyclophosphamide and dexamethasone or RVD. The treatment should be tailored to the individual. Bortezomib should be avoided in patients with neuropathies, although once-weekly dosing can potentially reduce additional neuropathy.⁶⁰ As lenalidomide is excreted renally, doses of lenalidomide should be adjusted in patients with renal insufficiency to avoid adverse effects. Thalidomide can increase the risk of venous thromboembolism.⁶¹ Thus, systemic anticoagulation or a low-dose aspirin regimen are necessary to reduce the risk of venous thromboembolism.⁶² In patients aged > 75 years, doses of chemotherapy should be reduced (Table 2).^{41,56,63–75} Additional reductions may be necessary, especially in frail individuals.

Some evidence now suggests that continuous therapy may improve survival in the elderly. In the MM-015 phase III trial, patients (aged > 65 years) received MP, MPR, or MPR followed by lenalidomide maintenance (10 mg/day, days 1–21 of a 28-day cycle).⁵⁴ The addition of lenalidomide maintenance to MPR significantly reduced the risk of progression (HR 0.34; $P < 0.001$). Similar results were seen in patients aged > 75 years, although the number of patients in this subgroup was small.⁷⁶ A second study compared bortezomib plus prednisone with bortezomib plus thalidomide maintenance therapy after induction with the three-drug combinations, bortezomib plus thalidomide and prednisone, or bortezomib plus MP in patients aged ≥ 65 years.⁷⁷ Both therapies were well tolerated, with no grade ≥ 3 hematologic toxicities, and 2% and 7% grade 3 peripheral neuropathy in the bortezomib plus prednisone and bortezomib plus thalidomide cohorts, respectively. There was no difference between the two cohorts in terms of PFS (median 35 months) and 3-year survival (70%). Thus, maintenance therapy with novel agents is tolerable and may improve outcomes in elderly patients.

CONCLUSION

Significant advances have been made in the prognosis, monitoring and treatment of MM. Novel agents have shown improved rates of response, PFS and, in some circumstances, OS. Many current studies show promising results, but the data are still maturing. The best combinations and sequences of therapies are still disputed, although lenalidomide- and bortezomib-based therapies have been extremely promising in the initial management of both transplantation-eligible and -ineligible patients. Extended treatment with novel agents may provide sustained

Table 1. Challenges in treating elderly patients

Challenges	Considerations
Comorbidities	
Renal	Lenalidomide may need dose adjustment and close monitoring
Hepatic	Dose reduction of bortezomib
Cardiac	More sensitive to fluid status, may need to reduce dexamethasone
Bone marrow insufficiency	Exacerbation of treatment-related cytopenias
Polyneuropathy	Avoid bortezomib or thalidomide
Venous thromboembolic events	Requires full-dose anticoagulation
Decreased functional capacity and frailty	
Low performance status	Correlates with increased toxicity from chemotherapy
Cognitive dysfunction	Require dose attenuation and close monitoring
Fear of falling	Higher risk for delirium, increased caregiver support
Slow gait speed	Provide preventative measure
Impaired ambulation	Consider neuropathy, proximal myopathy—dose or regimen modification
	May need to consider transportation needs, oral versus intravenous therapy and scheduling
Polypharmacy	Need to consider interactions
Decreased capacity to tolerate toxicity	Dose modifications

Table 2. Suggested dose reductions for elderly patients

Drug	Aged 65–75 years	Aged > 75 years	Further dose reduction
Dexamethasone	40 mg/day given orally on days 1–4 and 15–18 of each 28-day cycle, or 40 mg/day given orally on days 1, 8, 15 and 22 of each 28-day cycle ⁴¹	40 mg/day given orally on days 1, 8, 15 and 22 of each 28-day cycle ⁴¹	20 mg/day given orally on days 1, 8, 15 and 22 of each 28-day cycle ⁶⁴
Melphalan	0.25 mg/kg given orally on days 1–4 every 6 weeks ⁶⁵	0.25 mg/kg given orally on days 1–4 every 6 weeks; ⁶⁵ or 0.18 mg/kg given orally on days 1–4 of each 28-day cycle ⁶⁶	0.18 mg/kg given orally on days 1–4 every 6 weeks, or 0.13 mg/kg given orally on days 1–4 of each 28-day cycle
Cyclophosphamide	300 mg/m ² given orally on days 1, 8, 15 and 22 of each 28-day cycle ⁶⁷	300 mg/m ² given orally on days 1, 8 and 15, of each 28-day cycle; ⁶⁸ or 50 mg/day given orally on days 1–21 of each 28-day cycle	50 mg/day given orally on days 1–21 of each 28-day cycle, or 50 mg every other day given orally on days 1–21 of each 28-day cycle
Thalidomide	200 mg/day given orally continuously ⁶⁵	100 mg/day ⁶⁹ or 200 mg/day ^{65,70} given orally continuously	50 mg/day ⁶⁸ to 100 mg/day ^{69,71} given orally continuously
Lenalidomide	25 mg/day given orally on days 1–21 of each 28-day cycle ^{41,72,73}	15–25 mg/day given orally on days 1–21 of each 28-day cycle ^{41,72,73}	10–25 mg/day given orally on days 1–21 of each 28-day cycle ⁴¹
Bortezomib	1.3 mg/m ² given as bolus intravenous infusion on days 1, 4, 8 and 11 every 3 weeks ^{56,74}	1.3 mg/m ² given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks; ^{56,74} or 1.3 mg/m ² given as bolus intravenous infusion on days 1, 8, 15, and 22 every 5 weeks ⁷⁵	1.0–1.3 mg/m ² given as bolus intravenous infusion on days 1, 8, 15 and 22 every 5 weeks ⁷⁵

From Palumbo A, Anderson K. Multiple myeloma, *New England Journal of Medicine*, 364, 1046–1060. Copyright (2011) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.⁶³

disease control and delay relapse while maintaining quality of life. Promising strategies include consolidation or maintenance therapy following ASCT, or maintenance monotherapy for transplantation-ineligible patients. Use of novel agents to delay progression from smoldering MM to symptomatic MM is another promising strategy for optimizing outcomes through continuous therapy. Additional work is needed to determine the benefit of these approaches. Each of the three novel agents has a distinct safety profile that must be taken into consideration, although most adverse events can be managed with some combination of prophylaxis (for example, thromboprophylaxis for thalidomide and lenalidomide), dose modifications (for example, for lenalidomide-related myelosuppression) and careful patient selection (for example, avoiding use of thalidomide or bortezomib in patients with existing neuropathy). Another major concern, especially in the current political and economic climate, is the cost-effectiveness of novel agents when compared with early therapies. A balance between efficacy, safety and health-care costs needs to be reached, especially as the next generation of proteasome inhibitors and immunomodulators are being developed.

CONFLICT OF INTEREST

SG has no conflicts of interest to report. NM serves on advisory committees for Millenium, Celgene, Onyx and Merck. NM also owns equity in OncoPep.

ACKNOWLEDGEMENTS

NM was supported by a grant from the Department of Veterans Affairs Merit Review Award I01-BX001584 and the National Institutes of Health grants RO1-124929, PO1-155258, P50-100007 and PO1-78378M.

REFERENCES

- Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin* 2000; **50**: 7–33.
- Palumbo A, Rajkumar SV. Treatment of newly diagnosed myeloma. *Leukemia* 2009; **23**: 449–456.
- Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W et al. (eds) *SEER Cancer Statistics Review, 1975–2008*. National Cancer Institute: Bethesda, MD http://seer.cancer.gov/csr/1975_2008/, based on the November 2010 SEER data submission, posted to the SEER website, 2011.
- Brenner H, Gondas A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood* 2008; **111**: 2521–2526.
- Lokhorst H, Einsele H, Vesole D, Bruno B, San Miguel J, Pérez-Simon JA et al. International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. *J Clin Oncol* 2010; **28**: 4521–4530.
- Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008; **111**: 2516–2520.
- Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003; **78**: 21–33.
- Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, Chanan-Khan A et al. Consensus recommendations for standard investigative workup: report of the International Myeloma Working Group Consensus Panel 3. *Blood* 2011; **117**: 4701–4705.
- Engelhardt M, Kleber M, Udi J, Wäsch R, Spencer A, Patriarca F et al. Consensus statement from European experts on the diagnosis, management, and treatment of multiple myeloma: from standard therapy to novel approaches. *Leuk Lymphoma* 2010; **51**: 1424–1443.
- Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J et al. International staging system for multiple myeloma. *J Clin Oncol* 2005; **23**: 3412–3420.
- Dimopoulos MA, Barlogie B, Smith TL, Alexanian R. High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple myeloma. *Ann Intern Med* 1991; **115**: 931–935.
- Avet-Loiseau H, Attal M, Moreau P, Charbonnel C, Garban F, Hulin C et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood* 2007; **109**: 3489–3495.
- Fonseca R, Blood E, Rue M, Harrington D, Oken MM, Kyle RA et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood* 2003; **101**: 4569–4575.
- Kapoor P, Kumar S, Fonseca R, Lacy MQ, Witzig TE, Hayman SR et al. Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. *Blood* 2009; **114**: 518–521.
- Jagannath S, Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA et al. Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials. *Leukemia* 2007; **21**: 151–157.
- Dispenzieri A, Kyle R, Merlini G, Miguel JS, Ludwig H, Hajek R et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. *Leukemia* 2009; **23**: 215–224.
- Beetham R, Wassell J, Wallage MJ, Whiteway AJ, James JA. Can serum free light chains replace urine electrophoresis in the detection of monoclonal gammopathies? *Ann Clin Biochem* 2007; **44**: 516–522.
- Katzmann JA, Dispenzieri A, Kyle RA, Snyder MR, Plevak MF, Larson DR et al. Elimination of the need for urine studies in the screening algorithm for

- monoclonal gammopathies by using serum immunofixation and free light chain assays. *Mayo Clin Proc* 2006; **81**: 1575–1578.
- 19 Rajkumar SV, Kyle RA, Therneau TM, Melton 3rd LJ, Bradwell AR, Clark RJ *et al*. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood* 2005; **106**: 812–817.
 - 20 Dispenzieri A, Kyle RA, Katzmann JA, Therneau TM, Larson D, Benson J *et al*. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* 2008; **111**: 785–789.
 - 21 van Rhee F, Bolejack V, Hollmig K, Pineda-Roman M, Anaissie E, Epstein J *et al*. High serum-free light chain levels and their rapid reduction in response to therapy define an aggressive multiple myeloma subtype with poor prognosis. *Blood* 2007; **110**: 827–832.
 - 22 Snozek CL, Katzmann JA, Kyle RA, Dispenzieri A, Larson DR, Therneau TM *et al*. Prognostic value of the serum free light chain ratio in newly diagnosed myeloma: proposed incorporation into the international staging system. *Leukemia* 2008; **22**: 1933–1937.
 - 23 Munshi NC, Anderson KC, Bergsagel PL, Shaughnessy J, Palumbo A, Durie B *et al*. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood* 2011; **117**: 4696–4700.
 - 24 Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefeld JM *et al*. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 2007; **356**: 2582–2590.
 - 25 Pérez-Persona E, Vidriales MB, Mateo G, García-Sanz R, Mateos MV, de Coca AG *et al*. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood* 2007; **110**: 2586–2592.
 - 26 Wang M, Alexanian R, Delasalle K, Weber D. Abnormal MRI of spine is the dominant risk factor for early progression of asymptomatic multiple myeloma. *Blood* 2003; **102**: (abstract 2546).
 - 27 Hjorth M, Hellquist L, Holmberg E, Magnusson B, Rödger S, Westin J. Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I—a randomized study. Myeloma Group of Western Sweden. *Eur J Haematol* 1993; **50**: 95–102.
 - 28 Barlogie B, van Rhee F, Shaughnessy Jr JD, Epstein J, Yaccoby S, Pineda-Roman M *et al*. Seven-year median time to progression with thalidomide for smoldering myeloma: partial response identifies subset requiring earlier salvage therapy for symptomatic disease. *Blood* 2008; **112**: 3122–3125.
 - 29 Mateos MV, López-Corral L, Hernández M, Giraldo P, De La Rubia J, de Arriba F *et al*. Smoldering multiple myeloma (SMM) at high-risk of progression to symptomatic disease: a phase III, randomized, multicenter trial based on lenalidomide-dexamethasone (Len-Dex) as induction therapy followed by maintenance therapy with Len alone vs no treatment. *Blood* 2010; **116**: (abstract 1935).
 - 30 Haessler J, Shaughnessy Jr JD, Zhan F, Crowley J, Epstein J, van Rhee F *et al*. Benefit of complete response in multiple myeloma limited to high-risk subgroup identified by gene expression profiling. *Clin Cancer Res* 2007; **13**: 7073–7079.
 - 31 Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. *Blood* 2011; **118**: 3205–3211.
 - 32 Bladé J, Rosiñol L, Cibeira MT, Rovira M, Carreras E. Hematopoietic stem cell transplantation for multiple myeloma beyond 2010. *Blood* 2010; **115**: 3655–3663.
 - 33 Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF *et al*. A prospective randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. *N Engl J Med*. 1996; **335**: 91–97.
 - 34 Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K *et al*. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003; **348**: 1875–1883.
 - 35 Koreth J, Cutler CS, Djulbegovic B, Behl R, Schlossman RL, Munshi NC *et al*. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. *Biol Blood Marrow Transplant* 2007; **13**: 183–196.
 - 36 Stewart AK, Richardson PG, San-Miguel JF. How I treat multiple myeloma in younger patients. *Blood* 2009; **114**: 5436–5443.
 - 37 Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini D *et al*. Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. *Blood* 2005; **106**: 35–39.
 - 38 Vogl DT, Liu SV, Chong EA, Luger SM, Porter DL, Schuster SJ *et al*. Post-transplant outcomes of induction therapy for myeloma: thalidomide and dexamethasone versus doxorubicin, vincristine, and dexamethasone prior to high-dose melphalan with autologous stem cell support. *Am J Hematol* 2007; **82**: 1071–1075.
 - 39 Lokhorst HM, Schmidt-Wolf I, Sonneveld P, van der Holt B, Martin H, Barge R *et al*. Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. *Haematologica* 2008; **93**: 124–127.
 - 40 Gay F, Hayman SR, Lacy MQ, Buadi F, Gertz MA, Kumar S *et al*. Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients. *Blood* 2010; **115**: 1343–1350.
 - 41 Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME *et al*. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol* 2010; **11**: 29–37.
 - 42 Cavallo F, Brinchen S, Milone G, Ben-Yehuda D, Nagler A, Calabrese E *et al*. Stem cell mobilization in patients with newly diagnosed multiple myeloma after lenalidomide induction therapy. *Leukemia* 2011; **25**: 1627–1631.
 - 43 Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M *et al*. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol* 2010; **28**: 4621–4629.
 - 44 Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS *et al*. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood* 2010; **116**: 679–686.
 - 45 Kumar SK, Flinn I, Noga SJ, Hari P, Rifkin R, Callander N *et al*. Bortezomib, dexamethasone, cyclophosphamide and lenalidomide combination for newly diagnosed multiple myeloma: phase 1 results from the multicenter EVOLUTION study. *Leukemia* 2010; **24**: 1350–1356.
 - 46 Einsele H, Liebisch P, Langer C, Kropff M, Wandt H, Jung W *et al*. Velcade, intravenous cyclophosphamide and dexamethasone (VCD) induction for previously untreated multiple myeloma (German DSMM XIa Trial). *Blood* 2009; **114**: (abstract 131).
 - 47 Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M *et al*. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet* 2010; **376**: 2075–2085.
 - 48 Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T *et al*. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012; **366**: 1782–1791.
 - 49 McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG *et al*. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012; **366**: 1770–1781.
 - 50 Kapoor P, Rajkumar SV, Dispenzieri A, Gertz MA, Lacy MQ, Dingli D *et al*. Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant ineligible patients with multiple myeloma: a meta-analysis. *Leukemia* 2011; **25**: 689–696.
 - 51 Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Szubert AJ *et al*. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. *Blood* 2011; **118**: 1231–1238.
 - 52 Gay F, Vincent Rajkumar S, Falco P, Kumar S, Dispenzieri A, Petrucci MT *et al*. Lenalidomide plus dexamethasone vs. lenalidomide plus melphalan and prednisone: a retrospective study in newly diagnosed elderly myeloma. *Eur J Haematol* 2010; **85**: 200–208.
 - 53 Gay F, Rajkumar SV, Coleman M, Kumar S, Mark T, Dispenzieri A *et al*. Clarithromycin (Biaxin)-lenalidomide-low-dose dexamethasone (BiRd) versus lenalidomide-low-dose dexamethasone (Rd) for newly diagnosed myeloma. *Am J Hematol* 2010; **85**: 664–669.
 - 54 Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J *et al*. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med* 2012; **366**: 1759–1769.
 - 55 Niesvizky R, Jayabalan DS, Christos PJ, Furst JR, Naib T, Ely S *et al*. BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naïve symptomatic multiple myeloma. *Blood* 2008; **111**: 1101–1109.
 - 56 San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M *et al*. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008; **359**: 906–917.
 - 57 Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O *et al*. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol* 2010; **28**: 2259–2266.
 - 58 Palumbo A, Brinchen S, Petrucci MT, Musto P, Rossini F, Nunzi M *et al*. Intermediate-dose melphalan improves survival of myeloma patients

- aged 50 to 70: results of a randomized controlled trial. *Blood* 2004; **104**: 3052–3057.
- 59 Palumbo A, Sezer O, Kyle R, Miguel JS, Orlowski RZ, Moreau P *et al*. International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation. *Leukemia* 2009; **23**: 1716–1730.
- 60 Palumbo A, Mateos MV, Bringhen S, San Miguel JF. Practical management of adverse events in multiple myeloma: can therapy be attenuated in older patients? *Blood Rev* 2011; **25**: 181–191.
- 61 Hicks LK, Haynes AE, Reece DE, Walker IR, Herst JA, Meyer RM *et al*. A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma. *Cancer Treat Rev* 2008; **34**: 442–452.
- 62 Palumbo A, Cavo M, Bringhen S, Zamagni E, Romano A, Patriarca F *et al*. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *J Clin Oncol* 2011; **29**: 986–993.
- 63 Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med* 2011; **364**: 1046–1060.
- 64 Palumbo A, Gay F. How to treat elderly patients with multiple myeloma: combination of therapy or sequencing. *Hematology Am Soc Hematol Educ Program* 2009, 566–577.
- 65 Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B *et al*. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 2007; **370**: 1209–1218.
- 66 Palumbo A, Falco P, Benevolo G, Rossi D, Carella AM, Guglielmelli T *et al*. A multicenter, open label study of oral lenalidomide and prednisone (RP) followed by oral lenalidomide melphalan and prednisone (MPR) and oral lenalidomide maintenance in newly diagnosed elderly multiple myeloma patients. *Blood* 2010; **116**: (abstract 1940).
- 67 Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Hentz J *et al*. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia* 2009; **23**: 1337–1341.
- 68 Morgan GJ, Jackson GH, Davies FE, Drayson MT, Owen RG, Gregory WM *et al*. Maintenance thalidomide may improve progression free but not overall survival: results from the Myeloma IX maintenance randomisation. *Blood* 2008; **112**: (abstract 656).
- 69 Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V *et al*. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet* 2006; **367**: 825–831.
- 70 Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Sinnige H, Zweegman S *et al*. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. *J Clin Oncol* 2010; **28**: 3160–3166.
- 71 Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C *et al*. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *J Clin Oncol* 2009; **27**: 3664–3670.
- 72 Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A *et al*. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007; **357**: 2123–2132.
- 73 Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA *et al*. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007; **357**: 2133–2142.
- 74 Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T *et al*. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005; **352**: 2487–2498.
- 75 Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R *et al*. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol* 2010; **28**: 5101–5109.
- 76 Palumbo A, Adam Z, Kropff M, Foà R, Catalano J, Gisslinger H *et al*. A phase 3 study evaluating the efficacy and safety of lenalidomide (Len) combined with melphalan and prednisone followed by continuous lenalidomide maintenance (MPR-R) in patients (pts) $\geq$ 65 years (yrs) with newly diagnosed multiple myeloma (NDMM): updated results for pts aged 65–75 yrs enrolled in MM-015. *Blood* 2011; **118**: (abstract 475).
- 77 Mateos MV, Oriol A, Martínez-López J, Gutiérrez N, Teruel AI, de Paz R *et al*. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol* 2010; **11**: 934–941.