



available at www.sciencedirect.com



journal homepage: www.elsevierhealth.com/journals/ctrv



NEW DRUGS

Lenalidomide: A new therapy for multiple myeloma

Antonio Palumbo ^{a,*}, Jesús San Miguel ^{b,h}, Pieter Sonneveld ^{c,i},
Philippe Moreau ^{d,j}, Johannes Drach ^{e,k}, Gareth Morgan ^{f,l},
Hermann Einsele ^{g,m}

^a Department of Hematology, University of Torino, Ospedale Molinette, Via Genova 3, 10126 Torino, Italy

^b Hematology Department, University Hospital of Salamanca, Paseo San Vicente 58-182, 37007 Salamanca, Spain

^c Department of Hematology, Erasmus Medical Center, P.O. Box 2040, 3000 CA Rotterdam, Netherlands

^d Hematology Department, University Hospital, Centre Hospitalier Universitaire Hôtel-Dieu, Place Alexis Ricordeau, 44093 Nantes Cedex 01, France

^e Department of Medicine I, Clinical Division of Oncology, Medical University Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

^f Department of Haemato-oncology, The Royal Marsden Hospital, Down Road Sutton, Surrey SM2 5PT, UK

^g Medizinischen Klinik und Poliklinik II, Hämatologie und Onkologie, Universität Würzburg, Klinikstraße 6-8, 97070 Würzburg, Germany

Received 24 October 2007; received in revised form 5 December 2007; accepted 11 December 2007

KEYWORDS

Lenalidomide;
Multiple myeloma;
Dexamethasone;
Immunomodulatory
drugs

Summary The last decade has seen rapid evolution in the management of multiple myeloma. Cytogenetic, molecular, and proteomic techniques have led to a better understanding of the pathophysiology and prognostic markers of this heterogeneous malignancy. New immunomodulatory drugs, such as lenalidomide, which interrupt myeloma growth and survival pathways have entered into clinical usage. Combined with dexamethasone, oral lenalidomide has proved to be highly effective in patients whose disease has become resistant to conventional therapy. Currently, several clinical trials are ongoing in order to define the optimal use of this new agent and its combinations across the spectrum of patients with myeloma. Whether the ultimate outcome of future research will be a single-treatment solution for all patients, or whether

* Corresponding author. Tel.: +39 (011) 6336107; fax: +39 (011) 6963737.

E-mail addresses: appalumbo@yahoo.com (A. Palumbo), sanmigiz@aida.usal.es (J.S. Miguel), p.sonneveld@erasmusmc.nl (P. Sonneveld), philippe.moreau@chu-nantes.fr (P. Moreau), johannes.drach@meduniwien.ac.at (J. Drach), gareth.morgan@icr.ac.uk (G. Morgan), einsele_h@klinik.uni-wuerzburg.de (H. Einsele).

^h Tel.: +34 923 291384; fax: +34 923 294624.

ⁱ Tel.: +31 10 463 3123; fax: +31 10 463 5814.

^j Tel.: +33 240083271; fax: +33 240083250.

^k Tel.: +43 1 40400 4429; fax: +43 1 40400 4461.

^l Tel.: +44 (020) 8722 4130; fax: +44 (020) 8722 4432.

^m Tel.: +49 (312) 0170011; fax: +49 (312) 01 70730.

treatments will become better-tailored to the individual (based on prognostic markers and pre-existing co-morbidities) has yet to be determined.
© 2007 Elsevier Ltd. All rights reserved.

Introduction

Multiple myeloma (MM) is a haematological malignancy characterised by proliferating plasma cells in the bone marrow, with subsequent over-production of a monoclonal protein in most patients.^{1,2} MM accounts for 1.5–2% of all cancer deaths and approximately 20% of deaths from haematological malignancies.³ Although MM is initially sensitive to conventional chemotherapy, it remains incurable with almost all patients eventually relapsing. The median overall survival achieved with conventional approaches is approximately 33 months.^{4,5} High-dose melphalan and autologous stem-cell transplantation (ASCT) increase the rate of complete remission, and extend event-free survival and overall survival in selected patients. However, relapse rates are high and, until recently, there were few salvage therapies. With the advent of biologically-based treatment strategies such as bortezomib, thalidomide, and lenalidomide, treatments are now available which specifically target myeloma

cell interactions within the bone marrow microenvironment. These interactions are key to the growth and survival of malignant cells, and have proved to be powerful tools in overcoming drug resistance and prolonging the duration of response in patients with MM.^{6,7}

Lenalidomide (Revlimid®; Celgene, NJ, USA) is an oral immunomodulatory derivative of thalidomide with potent activity, but a different toxicity profile to the parent compound. It possesses pleiotropic (immunomodulatory, anti-angiogenic, and antineoplastic) activities, as well as anti-inflammatory effects.^{7,8} Lenalidomide induces apoptosis, decreases the binding of MM cells to bone marrow stromal cells, and inhibits the production of cytokines (e.g. interleukin-6, vascular endothelial growth factor, tumour necrosis factor alpha) in the bone marrow milieu, which mediate angiogenesis and the growth and survival of resistant MM cells (Fig. 1).⁹ It also enhances dexamethasone cytotoxicity, stimulates host anti-MM natural killer cell immunity, and inhibits osteoclast differentiation.^{10,11}

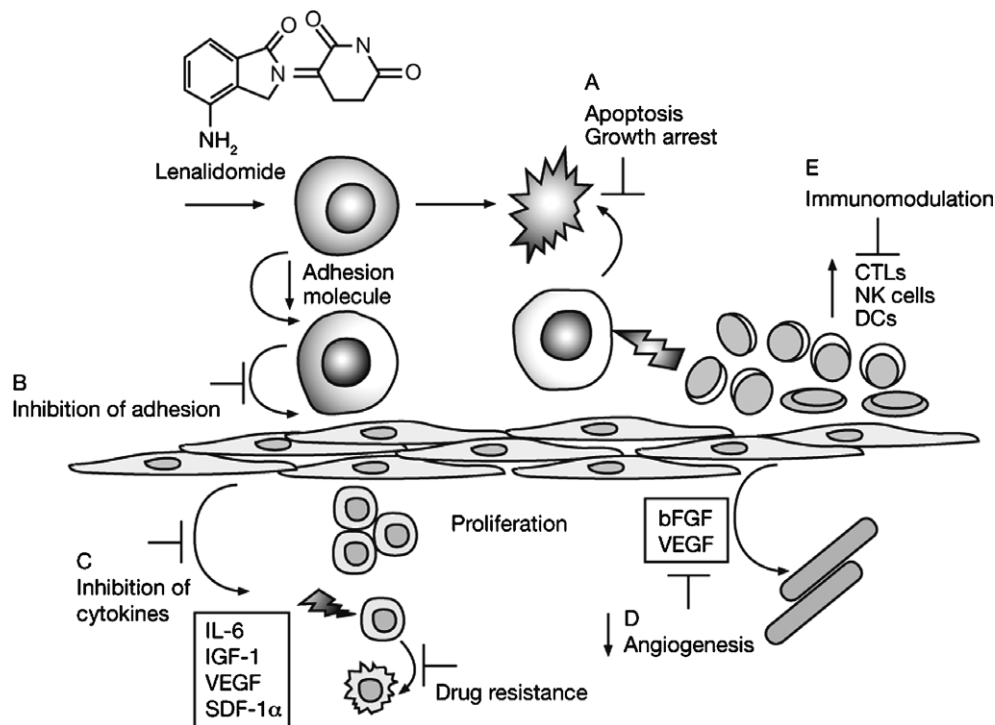


Figure 1 Antitumour activity of lenalidomide against multiple myeloma (MM) cells in the bone marrow microenvironment. A: Direct cytotoxicity of MM cells by causing G1 growth arrest or apoptosis. B: Inhibiting adhesion of MM cells to bone marrow stromal cells. C: Inhibiting the expression or bioactivity of interleukin (IL)-6, and other cytokines (e.g. vascular endothelial growth factor [VEGF], insulin-like growth factor [IGF-1], stromal cell-derived factor 1 [SDF-1 α]) necessary for cytokine-mediated growth, survival (proliferation, cell cycle progression), drug resistance (anti-apoptosis), and migration of MM cells within the bone marrow milieu. D: Inhibiting the production of VEGF and basic fibroblast growth factor (bFGF) necessary for angiogenesis. E: Providing co-stimulatory action on primary human T-cells, which enhance antitumour activity, mediated by T helper-1 cells, cytokines IL-2 and interferon- γ , and increases the number and function of natural killer (NK) cells, cytotoxic T-cells (CTLs) and dendritic cells (DCs). Figure reproduced from Expert Rev Anticancer Ther 2006;6(9):1239–1247 with permission of Future Drugs Ltd.⁹

Recently, lenalidomide has been found to have a direct anti-proliferative effect on MM cell lines (via p21WAF-1 up-regulation), while protecting normal B-cells from apoptosis, suggesting a potential role in bone marrow regeneration.¹²

This paper reviews the recent clinical findings with lenalidomide, an agent which has demonstrated remarkable activity against resistant MM cells.^{6,7} Lenalidomide has been approved by the Food and Drug Administration (FDA) in the USA, and the European Medicines Agency for use in combination with dexamethasone in patients with MM who have received at least one prior therapy.

Relapsed/refractory MM

Lenalidomide as a single agent

Two phase I dose-escalation trials of oral lenalidomide in advanced MM defined 25 mg/day as the maximum tolerated dose.^{10,13} These studies revealed the favourable pharmacokinetic profile and the acceptable toxicity profile of lenalidomide in patients with relapsed/refractory disease. In a subsequent phase II study, 25% of patients with relapsed/refractory MM responded to lenalidomide (complete response [CR], partial response [PR], or minor response). In patients who failed to respond to lenalidomide monotherapy, after the addition of oral dexamethasone 29% responded. In this study, the efficacy of lenalidomide was observed in heavily pre-treated patients, including those who had received prior treatment with thalidomide.¹⁴

Lenalidomide plus dexamethasone

Recently, two phase III randomized clinical trials (MM-009 and MM-010) have demonstrated the superiority of lenalidomide plus dexamethasone, compared with dexamethasone alone in previously treated patients with relapsed/refractory MM (Table 1).^{15,16}

In the first of these two trials (MM-009), researchers in the USA and Canada enrolled 354 patients.¹⁵ Two-thirds of the patients had previously had a stem cell transplant, and nearly half had previously been treated with thalidomide. Patients received either oral lenalidomide (25 mg/day on Days 1–21, of every 28-day cycle) plus dexamethasone (40 mg/day on Days 1–4, 9–12, and 17–20, of every cycle), or placebo plus dexamethasone (same dose and regimen as in the lenalidomide group) (Table 1). At the start of cycle 5, the dose of dexamethasone was reduced to 40 mg/day on Days 1–4 only, of every cycle. The study found that the time-to-progression (TTP) of disease was delayed in patients who had received lenalidomide plus dexamethasone, compared with those treated with dexamethasone alone (median 11.1 months vs 4.7 months, respectively; $p < 0.001$). Also improved in patients treated with lenalidomide plus dexamethasone, compared with those treated with dexamethasone alone, were overall response rate (61.0% vs 19.9%, respectively; $p < 0.001$) and median overall survival (29.6 months vs 20.2 months, respectively; $p < 0.001$).¹⁵

In a second study (MM-010), paralleling the findings from the North American trial, researchers from Europe, Israel, and Australia enrolled 351 patients.¹⁶ In this study, the

Table 1 Summary of clinical trials with lenalidomide combination treatment in the management of relapsed/refractory multiple myeloma

Therapy	n	Median age, years (range)	≥PR, %	CR, %	Median PFS, months	Median OS, months	Peripheral neuropathy grade 3–4, %	VTE grade 3–4, %	Neutropenia grade 3–4, %	Thrombocytopenia grade 3–4, %	Infection grade 3–4, %
Len + Dex ¹⁵	177	64 (36–86)	61	14	30	30	2	15	41	15	22
Len + Dex ¹⁶	176	63 (33–84)	60	16	NR	NR	11	11	30	11	10
Len + DVd ⁴¹	62	62	75	15	12	NR	5	9	32	13	13
RAD ⁴²	61	64 (44–77)	82	8			0	2	Neutropenia/thrombocytopenia: 13		8
RCD ⁴³	21	59 (34–76)	65	5					Grade 4: 38 ^a		
Len + Bort ⁴⁴	38	60 (37–79)	39	3							

Bort = bortezomib; CR = complete response; Dex = dexamethasone; DVd = pegylated liposomal doxorubicin, vincristine and dexamethasone; Len = lenalidomide; NR = not reached; OS = overall survival; PFS = progression-free survival; PR = partial response; RAD = lenalidomide plus adriamycin and dexamethasone; RCD = lenalidomide plus cyclophosphamide and dexamethasone; VTE = venous thromboembolism.

^a Neutrophil count was managed with granulocyte-colony stimulating factor in 12 patients, dose reductions/interruptions of cyclophosphamide were needed in 10 patients, and of lenalidomide in 5 patients.

researchers found a similar response with lenalidomide plus high-dose dexamethasone compared with dexamethasone alone: the median TTP was 11.3 months vs 4.7 months, respectively ($p < 0.001$), the overall response rate was 60.2% vs 24.0% ($p < 0.001$), and the median overall survival was not reached in the lenalidomide plus dexamethasone arm vs 20.6 months in the dexamethasone alone arm ($p = 0.03$).¹⁶

Subgroup analyses of patients from these two phase III studies found that when lenalidomide plus dexamethasone was administered at the first relapse, the treatment response rate was higher (65% vs 58%) and the TTP longer (18 months vs 10 months), than when treatment was used later as salvage therapy.¹⁷ Thus, earlier treatment with lenalidomide may further improve the length of response duration. Another subgroup analysis has shown that regardless of prior thalidomide exposure, the TTP and overall response were consistently higher with lenalidomide plus dexamethasone treatment, compared with dexamethasone alone (prior thalidomide: 36 weeks and 54% vs 20 weeks and 14%, no prior thalidomide: 60 weeks and 65% vs 20 weeks and 28%).¹⁸ Even among those patients who were resistant to prior treatment with thalidomide, lenalidomide plus dexamethasone led to a high overall response rate (50%) and a longer TTP (31 weeks).¹⁸ A multivariate analysis found that previous exposure to thalidomide, the duration of MM disease, and the number of prior therapies were all predictors of a shorter TTP.¹⁹

At the start of treatment, several patient characteristics can predict poor survival including: thrombocytopenia (platelet count $< 150 \times 10^9/L$); serum albumin ≥ 3 mg/dL; serum calcium ≥ 11 mg/dL; and serum creatinine ≥ 2 mg/dL.⁴ Lenalidomide was shown to be predominantly eliminated via urinary excretion, and effects of lenalidomide are therefore dependent on renal function.²⁰ In patients with severe renal dysfunction (creatinine clearance < 30 mL/min), TTP and overall survival after lenalidomide plus dexamethasone treatment tended to be shorter, compared with patients with a better creatinine clearance (> 30 mL/min); these results were still significantly higher than for patients treated with dexamethasone alone.²¹ In patients with impaired renal function dose adjustments are required. Recently, recommendations for initial starting doses in these patients have been provided.²⁰

Recently recognised chromosomal changes, such as deletion of chromosome 13 (del 13), deletion of chromosome 17, and translocation of 4;14 (t[4;14]), have been found to be prognostic for a more unfavourable clinical course, and these findings are likely to find application in future risk-adaptive treatment strategies.²² A recent study from the University of Calgary, Canada, has found that patients with and without chromosomal changes (del 13 or t[4;14]) responded equally well to lenalidomide plus dexamethasone treatment, with little difference between the patient groups in either the response rate (CR + PR) or event-free survival.²³

Notably, neither advancing age (> 65 years) nor the inclusion of patients ineligible for ASCT had a significant impact on the treatment response with lenalidomide plus dexamethasone.^{24–27} Subgroup analysis from the phase III studies found that the same clinical benefit was achieved in both elderly (> 65 years) and younger (≤ 65 years) patients

in terms of the overall response (58.9% vs 60.9%, respectively). However, TTP and overall survival were slightly shorter in the young (11.0 months and 29.8 months, respectively) compared with the elderly (14.0 months and overall survival not reached, respectively);²⁴ similar results were also obtained in patients aged ≥ 75 years.²⁶ These findings are reflected in data from the Canadian Expanded Access Programme, which found that among the elderly and the young, there was little difference in PR (58% vs 56%, respectively; $p = 0.15$), progression-free survival (PFS; 43% vs 43%, respectively), or overall survival (74% vs 76%, respectively) following a median of 4 cycles (range 1–8) of treatment with lenalidomide plus dexamethasone, with or without prednisone.²⁷

Evidence from the phase III studies found that both previously-transplanted and non-transplanted patients achieved comparable rates of overall response (63% vs 55%, respectively) and CR (13% vs 16%, respectively) with lenalidomide plus dexamethasone treatment. However, there was a trend towards a slightly longer TTP in those without prior ASCT (median 10.3 months vs 14.3 months; $p = 0.13$).²⁵

Adverse events

While the phase III studies found that combining lenalidomide with high-dose dexamethasone was associated with more side effects than dexamethasone alone (19.8% vs 10.2%, respectively, of patients dropped out of the study because of side effects), this has to be considered in the context of the improved overall response rate. Only 38.4% of patients in the lenalidomide plus dexamethasone group withdrew from the study because of disease progression, compared with 71.6% of those taking dexamethasone alone.¹⁵

Lenalidomide is not associated with the same frequency or severity of side effects commonly seen with thalidomide, such as neuropathy, constipation, or somnolence. Myelosuppression (grade 3–4 neutropenia and thrombocytopenia), which was the dose-limiting side effect from phase I studies of lenalidomide, is the most frequent adverse event and can be effectively managed by dose reductions and interruptions. The incidence of grade 3–4 neutropenia (41.2% in the MM-009 study and 29.5% in the MM-010 study) was three-times higher than that of thrombocytopenia (14.7% in MM-009 and 11.4% in MM-010).^{15,16}

Notably, Richardson et al. observed that the proportion of patients who experienced grade 3–4 myelosuppression was significantly higher in patients who had received prior treatment with ASCT.¹⁴ This finding was confirmed by the phase III studies which found that the incidence of grade 3–4 neutropenia with lenalidomide plus dexamethasone was significantly higher in patients who had received prior ASCT (38.1% vs 27.3%; $p < 0.05$).²⁵ The risk of grade 3–4 myelosuppression, and thrombocytopenia in particular, following treatment with lenalidomide is also significantly increased in patients with impaired renal function^{21,28,29} emphasizing the need for appropriate dose reduction. Evidence from the Canadian Expanded Access Programme shows that treatment with lenalidomide plus dexamethasone (with or without prednisone) was equally well-toler-

ated in both elderly (>65 years) and young (\leq 65 years) patients with 46% and 49%, respectively, remaining on therapy after a median of 4 cycles (range 1–8) of treatment.²⁷ Regardless of age, among the elderly and young a similar incidence of grade 3–4 neutropenia (46% vs 44%, respectively), grade 3–4 thrombocytopenia (38% vs 24%), febrile neutropenia (12% vs 9%), infection (25% vs 16%), and grade 3–4 fatigue (13% vs 11%) was recorded, with no significant differences between the groups.²⁷

Since myelosuppression is common with lenalidomide treatment a group of experts have provided some clinical guidance for the management of cytopenias. In general, patients' blood count should be monitored on a biweekly basis during lenalidomide treatment, but weekly monitoring is recommended in patients with cytopenias at baseline.³⁰ In case cytopenias occur, granulocyte-colony stimulating factor (G-CSF) or erythropoietin stimulating agents might be needed, and in more severe cases dose reductions or interruptions might be required.³⁰ In addition, the group recommends the consideration of routine antibiotic prophylaxis for all patients upon initiation of lenalidomide treatment.³¹

While there is a benefit of the combination of lenalidomide and dexamethasone for the treatment of MM compared with lenalidomide as monotherapy,¹⁴ studies also show that the addition of dexamethasone increases the risk of deep-vein thrombosis. In the North American study (MM-009), grade 3–4 thromboembolic events occurred in 14.7% of patients treated with lenalidomide plus dexamethasone, and 3.4% of patients in the dexamethasone alone group.¹⁵ In the other study (MM-010), grade 3–4 thromboembolic events occurred in 11.4% of patients treated with lenalidomide plus dexamethasone and 4.5% of patients in the dexamethasone alone group.¹⁶ Additional studies have shown that the risk of a thrombotic event further increased in patients treated with lenalidomide, who had a history of prior thalidomide treatment, or concomitant erythropoietin use.^{18,32}

Also, both lenalidomide and thalidomide are associated with an increased risk of venous thromboembolism, particularly when used with high-dose dexamethasone. Across a number of studies in MM patients treated with lenalidomide plus dexamethasone, venous thromboembolism rates vary widely (3–75%).^{14,32–35} As a result, safety concerns persist for lenalidomide in MM despite FDA approval.³⁶ It should be remembered, however, that patients with MM are at relatively high baseline-risk of developing thromboembolic events, especially deep-vein thrombosis. Upfront combinations, including thalidomide plus low-dose dexamethasone and/or alkylating agents, are associated with intermediate risk, whereas the same regimens for relapsed/refractory MM seem to be associated with lower risk.³⁷ The risk of thromboembolic events may be particularly high when specific risk factors increase the thrombogenic potential of the immunomodulatory agents. These risk factors are: combinational regimen including doxorubicin or high-dose dexamethasone; newly diagnosed disease; immobilization; infection; and history of thromboembolism.^{32,37,38} National Comprehensive Cancer Network Guidelines recommend prophylactic anticoagulation in patients treated with lenalidomide plus dexamethasone.⁵ Several different thromboprophylaxis strategies have been effective in lowering the risk of developing clots: daily aspirin (81–325 mg/day);

full-intensity warfarin (International Normalized Ratio 2–3); and prophylactic subcutaneous enoxaparin (40 mg/day). However, none of these prevention strategies has been prospectively compared, so the choice often reflects physician and/or patient preference.^{34,37,36,39} A panel of experts recommend a 4- to 6-month course of prophylaxis in patients with risk factors, with low-dose aspirin (81–100 mg) or prophylactic doses of low-molecular-weight heparin.⁴⁰

Other lenalidomide combinations

The clinical safety and efficacy of lenalidomide in combination with other agents for the management of patients with relapsed/refractory MM has been evaluated in a number of clinical trials (Table 1). In a phase I/II clinical trial at the Cleveland Clinic Cancer Center, the combination of lenalidomide (10 mg/day, on Days 1–21) plus DVd, which comprised intravenous pegylated liposomal doxorubicin (40 mg/m²), intravenous vincristine (2 mg on Day 1), and oral dexamethasone (40 mg/day on Days 1–4) every 28-day cycle was evaluated. Overall, 41 of 62 patients included in the trial had failed a previous thalidomide-containing regimen. The lenalidomide plus DVd regimen was found to be well tolerated with a PR or better, recorded in 75% of patients (29% achieving a CR or near-CR) and a median PFS of 12 months.⁴¹ Myelosuppression was acceptable, with a 7% incidence of febrile neutropenia. Thromboembolic events were recorded in 9% of patients and grade 3 peripheral neuropathy in 5%.

Data of a phase I/II study evaluating the efficacy and safety of lenalidomide (15 mg for 21 days) used in combination with adriamycin (9 mg/m² for Days 1–4 as a continuous infusion) and dexamethasone (40 mg/day on Days 1–4 and 17–20) have also been presented. After two unexpected events of non-febrile neutropenia, the protocol was amended to include G-CSF support (6 mg of pegfilgrastim on Day 6), resulting in an uneventful course in all patients treated subsequently at the two highest dose levels of lenalidomide.⁴² Of the 22 patients evaluable for a response, a response (at least PR) was achieved in 18 patients (82%). These data provide evidence for the efficacy and acceptable toxicity profile of lenalidomide plus adriamycin and dexamethasone in the treatment of relapsed MM.¹⁸

In a second study, heavily pre-treated patients (median of previous lines of therapy 4 [range 1–8]) were treated with oral daily doses of lenalidomide (25 mg for 21 days of a 28-day cycle) in combination with dexamethasone (40 mg/day on Days 1–4 and 12–15) and cyclophosphamide (500 mg/day on Days 1, 8, 15, and 28) of for a maximum of 6 cycles. The study found that this combination was effective, and had a manageable toxicity profile. Of the 20 patients assessed, 15 patients achieved a response, including 1 CR and 3 very good partial responses (VGPR).⁴³ Only 2 patients discontinued treatment due to a failure to respond, and another patient discontinued due to liver toxicity. Neutrophil counts were maintained and managed by administration of G-CSF in 12 patients, a dose reduction or interruption of cyclophosphamide in 10 patients, and a dose reduction or interruption of lenalidomide in 5 patients. A further study is now ongoing to investigate this treatment regimen with cyclophosphamide on Days 1 and 8 only.

At the 2006 annual American Society of Hematology Meeting, Richardson et al. presented the results of the first study combining lenalidomide (5–15 mg/day) with bortezomib (1.0 or 1.3 mg/m²). The study, conducted in heavily pre-treated relapsed/refractory patients with MM (median prior therapies 5 [range 1–13]), found that the combination of lenalidomide plus bortezomib with or without dexamethasone achieved at least a minimal response rate of 58%, including a CR/near-CR in 6% of patients.⁴⁴ Responses were long-lasting (median 6 months, range 1–26) and 11 patients remained on therapy for more than 1 year. Additionally, preliminary data from a phase II trial of lenalidomide (15 mg/day) plus bortezomib (1.0 mg/m²) and dexamethasone (40 mg/day) demonstrated a 50% overall response rate. However, although dexamethasone dose reductions were needed in the majority of patients, the combination was otherwise well tolerated.⁴⁵

Newly diagnosed MM

Lenalidomide plus dexamethasone

A phase II trial was conducted to evaluate the efficacy and safety of lenalidomide plus dexamethasone as initial therapy for MM (Table 2). A total of 34 patients were enrolled and were treated with oral daily doses of lenalidomide (25 mg on Days 1–21 of each 28-day cycle) and dexamethasone (40 mg/day on Days 1–4, 9–12, and 17–20).^{46,47} For patients who continued therapy beyond 4 months, the dose of dexamethasone was reduced to 40 mg/day on Days 1–4 of each cycle only. Patients also received once-daily aspirin (81 mg or 325 mg, at the discretion of the physician) as thromboprophylaxis. Overall, 13 patients proceeded to ASCT after a median of 4 cycles of lenalidomide plus dexamethasone treatment (and were evaluated at that time), while 21 patients stayed on treatment for a median of 19 cycles (range 2–30).⁴⁶ The combination was found to be highly effective: the overall response rate was 91%; the CR or VGPR rate was 56%. Among the patients staying on the combination treatment as primary therapy without stem cell transplantation, the CR or VGPR rate was 67%.⁴⁶ Two-year PFS and the 3-year overall survival were 59% and 85%, respectively.⁴⁶ In the 13 patients who received ASCT the 2-year PFS was 83%, and the 3-year overall survival was 92% (Table 2).⁴⁶ Half of the patients had grade 3 or greater non-haematological toxicities (mostly fatigue).⁴⁶ Only 1 patient developed a pulmonary embolism (grade 4 toxicity) and recovered with therapy; no other thromboembolic events were recorded.⁴⁷ Overall, myelosuppression was minimal in this trial, probably reflecting the better bone marrow reserves in patients who had previously been untreated.⁴⁷ Furthermore, the researchers found no adverse effect on stem-cell mobilization, indicating that lenalidomide plus dexamethasone treatment would be useful as a pre-transplantation conditioning regimen.^{46,47} However, Kumar et al. reported a trend towards a lower CD34⁺ stem cell yield within 12 months of diagnosis in patients who received lenalidomide plus dexamethasone, and hence recommended that CD34⁺ stem cells be collected within 6 months of initiation of lenalidomide containing treatments.⁴⁸ It must be noted that this was a retrospective study, and that

Table 2 Summary of clinical trials with lenalidomide combination treatment in the management of newly diagnosed multiple myeloma

Therapy	n	Median age, years (range)	≥ PR, %	CR, %	Median PFS, months	Median OS, months	Peripheral neuropathy grade 3–4, %	VTE grade 3–4, %	Neutropenia grade 3–4, %	Thrombocytopenia grade 3–4, %	Infection grade 3–4, %
Len + Dex high-dose ⁴⁶	34	64 (32–78)	91	18	NR	88% at 3 years	3	3	21		8
Len + Dex low-dose ³⁵	445	65				97% at 1 year	6	6			
BiRD ⁴⁹	72	63 (36–83)	88	31	NR	NR	13	13	17	18	4
MPR ⁵⁰	54	71 (57–77)	81	24		100% at 1 year	6	6	52	24	10
MPR ⁵¹	7	74 (72–85)	71	14			14	14	43	14	

BiRD = lenalidomide plus dexamethasone and clarithromycin; CR = complete response; Dex = dexamethasone; Len = lenalidomide; MPR = lenalidomide plus melphalan and prednisone; NR = not reached; OS = overall survival; PFS = progression-free survival; PR = partial response; VTE = venous thromboembolism.

only 3 of the 43 patients failed to mobilize. These patients were all older than 67 years of age, and had received 7–11 months of therapy before the attempt at stem cell mobilization was made.⁴⁸

In a randomized phase III study (E4A03) the efficacy and safety of lenalidomide plus low-dose dexamethasone was compared with lenalidomide plus high-dose dexamethasone. The study enrolled 445 patients who were treated with lenalidomide (25 mg/day on Days 1–21 of each 28-day cycle) plus high-dose dexamethasone (40 mg/day on Days 1–4, 9–12, and 17–20 of every cycle), or lenalidomide plus low-dose dexamethasone (40 mg/day on Days 1, 8, 15, and 22 of every cycle). The study showed that overall survival at first interim analysis was significantly superior with lenalidomide plus low-dose dexamethasone, compared with lenalidomide plus high-dose dexamethasone (97% vs 86%, respectively; $p < 0.001$). Moreover, toxicities were higher with lenalidomide plus high-dose dexamethasone, compared with lenalidomide plus low-dose dexamethasone: the incidence of grade ≥ 3 thromboembolism (22.1% vs 6.1%); infection/pneumonia (15.7% vs 7.5%); and hyperglycaemia (9.7% vs 6.6%) (Table 2).³⁵

A second phase II trial evaluated the safety and efficacy of once-daily oral dosing with lenalidomide (25 mg on Days 1–21 of each 28-day cycle) in combination with dexamethasone (40 mg once weekly) and clarithromycin (500 mg twice daily) (Table 2).^{29,49} A total of 72 patients (54% of whom had International Staging System disease classification stage >2) were followed up for a mean of 10 months. Once again, the combination yielded a high overall response rate (88%) with 31% (achieving a CR or near-CR).⁴⁹ The study found that both myelosuppression and a baseline serum creatinine level of >1.4 mg/dL were highly predictive of a dose reduction.²⁹

Melphalan, prednisone, and lenalidomide

Based on the encouraging results from trials with lenalidomide plus dexamethasone combination therapy, phase I/II dose-finding studies were conducted to evaluate the safety and efficacy of lenalidomide used in combination with melphalan and prednisone, in newly diagnosed elderly patients who were not candidates for stem cell transplantation (Table 2).^{50,51} In the first of these studies, Palumbo et al. investigated 9 courses of treatment with oral lenalidomide (5–10 mg/day for 21 days every 4–6 weeks) used in combination with melphalan (0.18–0.25 mg/kg) and prednisone (2 mg/kg for 4 days every 4–6 weeks), followed by maintenance therapy with once-daily oral lenalidomide (10 mg/day for 21 days every 4–6 weeks).⁵⁰ Aspirin (100 mg/day) was used to prevent deep-vein thrombosis. The study found that this combination was well tolerated and effective in newly diagnosed elderly patients.⁵⁰ In all patients, a 1-year event-free survival of 92% and a 1-year overall survival of 100% was reported. At the maximum tolerated dose (0.18 mg/kg melphalan and 10 mg/day lenalidomide), 47.6% of patients achieved at least a VGPR and 23.8% a CR. Grade 3–4 adverse events were mainly related to haematological toxicities such as neutropenia (52.4%) and thrombocytopenia (23.8%). Severe non-haematological side effects were less frequent, and included febrile neutropenia (9.5%), cutaneous rash (9.5%), and thromboembolism

(5.8%). The addition of aspirin markedly reduced the risk of thromboembolic events in this study.⁵⁰

These findings were confirmed in a subsequent study which defined the maximum tolerated doses: as 5 mg/m² for melphalan, 60 mg/m² for prednisone, and 10 mg for lenalidomide.⁵¹ Notably, the results from Palumbo et al. showed that combination treatment with lenalidomide appeared to overcome the poor prognosis conferred by del 13 with event-free survival not significantly different between those who did and did not have this abnormality.⁵⁰ These results have been corroborated by Bahlis et al. who found that neither the presence of del 13 nor t(4;14) impacted on the response rates (71.5% vs 86.0%, respectively) or the event-free survival (71.4% vs 72.4%, respectively; $p = 0.66$) at 6 months.²³

Amyloidosis

Based on the encouraging results seen with lenalidomide in MM patients, a phase II trial was conducted in order to evaluate the haematological response rate and toxicity of lenalidomide monotherapy and lenalidomide plus dexamethasone combination, in patients with primary systemic amyloidosis.⁵² Overall, the experience in 23 patients found that lenalidomide monotherapy had limited activity in patients with primary systemic amyloidosis. Only 1 out of 22 patients achieved a haematological response after 3 cycles of treatment, and this patient continued on monotherapy to ultimately achieve both a renal and liver response.⁵² When dexamethasone was added to lenalidomide for the non-responders, 45% (10/22) achieved a response, including a haematological response in 41% (9/22) of patients, and an organ response (4 renal responses, 2 cardiac responses, and 2 liver responses) in 23% (5/22) of patients.^{52,53} The median time to a response was 6.2 months for a haematological response, and 9.4 months for an organ response. The most common grade 3–4 adverse events, possibly attributable to lenalidomide, were neutropenia (45%), thrombocytopenia (27%), fatigue (18%), and rash (18%).⁵² Another phase II trial showed a CR with lenalidomide monotherapy in 2 out of 24 evaluable patients, when dexamethasone was added to lenalidomide for the non-responders, an additional 5 patients achieved a CR. In all, the overall haematological response rate, obtained with either lenalidomide monotherapy or combination of lenalidomide and dexamethasone, was 67%.⁵⁴

Conclusions

Current evidence confirms that once-daily oral treatment with lenalidomide when combined with high-dose dexamethasone is an effective new treatment option for patients with recurrent/refractory MM, with a manageable adverse events profile.^{15,16} Regardless of whether patients had been previously treated with thalidomide, the lenalidomide plus dexamethasone combined regimen was more effective at stalling the progression of the disease than dexamethasone alone.¹⁸ In addition, it has been shown in newly diagnosed patients that combining lenalidomide with low-dose dexamethasone results in a clear benefit in overall survival and toxicity compared with the combination which includes high-dose dexamethasone.³⁵

Overall, 56% of newly diagnosed patients^{46,47} and 25% of patients with recurrent/refractory MM^{15,16} achieved a CR or VGPR indicating the profound cytoreduction that can be achieved by combining oral lenalidomide with dexamethasone. Subsequently, a CR or VGPR rate of 47.6% was reported with lenalidomide 10 mg/day used in combination with melphalan and prednisone in newly diagnosed elderly patients (>65 years).⁵⁰ Encouragingly, open-label trials have shown that patients appear to respond equally well to lenalidomide combination treatments, regardless of the presence or absence of prognostic markers for a more unfavourable clinical course (del 13 and t[4;14]).^{23,50}

The advent of a new era in new biological treatments has provided clinicians with some optimism that MM may ultimately become a highly treatable condition, associated with a prolonged survival and improved quality of life for patients. As our understanding of the pathogenesis of the disease improves, it is likely that molecular genetics will identify patterns of gene expression which will not only be used to define outcome, but also to identify new molecular targets for drug treatment and direct treatment decisions. In the interim, a plethora of clinical trials are now ongoing in order to optimise the use of this important new treatment modality.

Conflict of interest statement

A.P. is a speaker and advisory board member for both Celgene and Pharmion, and has received a research grant from Celgene. J.S.M. is an advisory board member for Celgene, Pharmion and Janssen-Cilag. P.S. and P.M. are speakers and advisory board members for Celgene. G.M. is an advisory board member for Celgene, Johnson & Johnson, Millennium and Novartis. H.E. is a speaker for Celgene and has received a research grant from Celgene.

Acknowledgements

The authors received editorial support from Excerpta Medica in the preparation of this manuscript, funded by Celgene. The authors, however, were fully responsible for content and editorial decisions for this manuscript.

References

- Bartlett JB, Tozer A, Stirling D, Zeldis JB. Recent clinical studies of the immunomodulatory drug (IMiD) lenalidomide. *Br J Cancer* 2005;**93**:613–9.
- Harousseau JL, Shaughnessy Jr J, Richardson P. Multiple myeloma. *Hematol Am Soc Hematol Educ Program*:237–56.
- Piazza FA, Gurrieri C, Trentin L, Semenzato G. Towards a new age in the treatment of multiple myeloma. *Ann Hematol* 2007;**86**:159–72.
- Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003;**78**:21–33.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™. Cancer-related fatigue. V.3.2007. Available from: <http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf> [accessed 26.09.07].
- Kumar S, Rajkumar SV. Thalidomide and lenalidomide in the treatment of multiple myeloma. *Eur J Cancer* 2006;**42**:1612–22.
- Kastritis E, Dimopoulos MA. The evolving role of lenalidomide in the treatment of hematologic malignancies. *Expert Opin Pharmacother* 2007;**8**:497–509.
- Richardson PG, Mitsiades C, Hideshima T, Anderson KC. Lenalidomide in multiple myeloma. *Expert Rev Anticancer Ther* 2006;**6**:1165–73.
- Raje N, Hideshima T, Anderson KC. Therapeutic use of immunomodulatory drugs in the treatment of multiple myeloma. *Expert Rev Anticancer Ther* 2006;**6**:1239–47.
- Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood* 2002;**100**:3063–7.
- Breitkreutz I, Vallet S, Raab MS, et al. Lenalidomide and bortezomib inhibit osteoclast differentiation and activation in multiple myeloma: clinical implications. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3485].
- Verhelle D, Corral LG, Wong K, et al. Lenalidomide and CC-4047 inhibit the proliferation of malignant B cells while expanding normal CD34+ progenitor cells. *Cancer Res* 2007;**67**:746–55.
- Zangari M, Barlogie B, Jacobson J, et al. Revlimid 25 mg (REV 25) × 20 versus 50 mg (REV 50) × 10 q 28 days with bridging of 5 mg × 10 versus 10 mg × 5 as post-transplant salvage therapy for multiple myeloma (MM). *Blood*:102. [Abstract 1642].
- Richardson PG, Blood E, Mitsiades CS, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood* 2006;**108**:3458–64.
- Weber DM, Chen C, Niesvizky R, et al. For the Multiple Myeloma-009 Study Investigators. Oral lenalidomide plus dexamethasone for relapsed/refractory multiple myeloma. *N Engl J Med* 2007;**357**:2133–42.
- Dimopoulos M, Spencer A, Attal M, et al. For the Multiple Myeloma-010 Study Investigators. Lenalidomide plus dexamethasone versus dexamethasone alone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;**357**:2123–32.
- Stadtmauer E, Weber D, Dimopoulos M, et al. Lenalidomide in combination with dexamethasone is more effective than dexamethasone at first relapse in relapsed multiple myeloma. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3552].
- Wang M, Knight R, Dimopoulos M, et al. Effect of Len/Dex in MM despite Thal resistance. *Haematologica* 2007;**92**(s2). [Abstract PO-662].
- Wang M, Knight R, Dimopoulos M, et al. Lenalidomide in combination with dexamethasone was more effective than dexamethasone in patients who have received prior thalidomide for relapsed or refractory multiple myeloma. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3553].
- Chen N, Lau H, Kong L, et al. Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. *J Clin Pharmacol* 2007;**47**(12):1466–75.
- Weber D, Wang M, Chen C, et al. Lenalidomide plus high-dose dexamethasone provides improved overall survival compared to high-dose dexamethasone alone for relapsed or refractory multiple myeloma (MM): results of 2 phase III studies (MM-009, MM-010) and subgroup analysis of patients with impaired renal function. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3547].
- Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergrroupe Francophone du Myélome. *Blood* 2007;**109**:3489–95.
- Bahlis NJ, Mansoor A, Lategan JC, et al. Lenalidomide overcomes poor prognosis conferred by deletion of chromosome 13

- and t(4;14) in multiple myeloma: MM016 trial. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3557].
24. Chanan-Khan AA, Weber D, Dimopoulos M, et al. Lenalidomide (L) in combination with dexamethasone (D) improves overall survival and time to progression in elderly patients (pts) with relapsed or refractory (rel/ref) multiple myeloma (MM). *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3551].
 25. Chanan-Khan AA, Yu Z, Weber D, et al. Lenalidomide (L) in combination with dexamethasone (D) improves time to progression (TTP) in non-stem cell transplant patients (pts) with relapsed or refractory (rel/ref) multiple myeloma (MM): analysis from MM-009 and MM-010 randomized phase III clinical trials. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3554].
 26. Lonial S, Knight R, Dimopoulos M, et al. Effect of Len/Dex in MM in different age groups. *Haematologica* 2007;**92**(s2). [Abstract PO-663].
 27. Reece DE, Masih-Khan E, Chen C, et al. Lenalidomide (Revlimid[®]) +/- corticosteroids in elderly patients with relapsed/refractory multiple myeloma. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3550].
 28. Reece DE, Masih-Khan E, Chen C, et al. Use of lenalidomide (Revlimid[®]) +/- corticosteroids in relapsed/refractory multiple myeloma patients with elevated baseline serum creatinine levels. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3548].
 29. Niesvizky R, Jayabalan DS, Zafar F, et al. Lenalidomide induced myelosuppression is potentially associated with renal dysfunction in treatment naïve myeloma (MM) patients receiving BiRD (Biaxin[®]/Revlimid[®]/Dexamethasone) combination therapy (Rx). *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3549].
 30. Sonneveld P, Dimopoulos M, San Miguel J, et al. Recommended management of cytopenia for len/dex in MM. *Haematologica/Hematol J* 2007;**92**(s2):217. [Abstract PO-1122].
 31. Attal M, Dimopoulos M, San Miguel J, et al. Management of non-haematological toxicity of len/dex. *Haematologica/Hematol J* 2007;**92**(s2):217–8. [Abstract PO-1123].
 32. Niesvizky R, Spencer A, Wang M, et al. Increased risk of thrombosis with lenalidomide in combination with dexamethasone and erythropoietin. *ASCO Meeting Abstracts* 2006;**24**. [Abstract 7506].
 33. Zonder JA, Durie BG, McCoy J, et al. High incidence of thrombotic events observed in patients receiving lenalidomide (L) + dexamethasone (D) (LD) as first-line therapy for multiple myeloma (MM) without aspirin (ASA) prophylaxis. *Blood (ASH Annual Meeting Abstracts)* 2005;**106**. [Abstract 3455].
 34. Bennett CL, Hussain Z, Courtney M, Yarnold P, Raisch D, McKoy JM. RADAR update on thalidomide (Thal)- and lenalidomide (Len)-associated venous thromboembolism (VTE): safety concerns persist for multiple myeloma (MM) despite FDA approvals in this setting. *Blood (ASH Annual Meeting Abstracts)* 2006;**108** [Abstract 3310].
 35. Rajkumar SV, Jacobus S, Callander N, Fonseca R, Vesole D, Williams M, Abonour R, Siegel D, Greipp P. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. *ASCO Annual Meeting Proceedings* 2007;**25**(18S) [Abstract LBA8025].
 36. Durie BG, Richardson P, Palumbo A, et al. Deep vein thrombosis in myeloma: estimate of prevalence and recommendations for therapy based upon a survey of members of the International Myeloma Working Group (IMWG). *Blood (ASH Annual Meeting Abstracts)* 2006;**108** [Abstract 3571].
 37. Zonder JA. Thrombotic complications of myeloma therapy. *Hematol Am Soc Hematol Educ Program*:348–55.
 38. Prandoni P. Acquired risk factors for venous thromboembolism in medical patients. *Hematol Am Soc Hematol Educ Program*: 458–61.
 39. Hirsh J. Risk of thrombosis with lenalidomide and its prevention with aspirin. *Chest* 2007;**131**:275–7.
 40. Palumbo A, Dimopoulos M, San Miguel J, et al. VTE management recommendations for len/dex in MM. *Haematologica/Hematol J* 2007;**92**(s2):217. [Abstract PO-1121].
 41. Baz R, Walker E, Karam MA, et al. Lenalidomide and pegylated liposomal doxorubicin-based chemotherapy for relapsed or refractory multiple myeloma: safety and efficacy. *Ann Oncol* 2006;**17**:1766–71.
 42. Knop S, Gerecke C, Topp MS, et al. RAD (Revlimid, Adriamycin, Dex) is a new treatment regimen for relapsed multiple myeloma. *Haematologica* 2007;**92**(s2). [Abstract PO-658].
 43. Morgan GJ, Schey SA, Wu P, et al. Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients. *Br J Haematol* 2007;**137**:268–9.
 44. Richardson PG, Jagannath S, Avigan DE, et al. Lenalidomide plus bortezomib (Rev-Vel) in relapsed and/or refractory multiple myeloma (MM): final results of a multicenter phase 1 trial. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 405].
 45. Richardson PG, Jagannath S, Raje N, et al. Phase 2 study of Rev/Vel/Dex in relapsed/refractory MM. *Haematologica* 2007;**92**(s2). [Abstract PO-660].
 46. Lacy MQ, Gertz MA, Dispenzieri A, et al. Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma. *Mayo Clin Proc* 2007;**82**:1179–84.
 47. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood* 2005;**106**:4050–3.
 48. Kumar S, Dispenzieri A, Lacy MQ, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. *Leukemia* 2007;**21**:2035–42.
 49. Niesvizky R, Jayabalan D, Zafar F, et al. BiRD (Biaxin[®]/Revlimid[®]/Dexamethasone) in myeloma (MM). *Haematologica* 2007;**92**(s2). [Abstract PO-714].
 50. Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA Italian Multiple Myeloma Network. *J Clin Oncol* 2007;**25**:4459–65.
 51. Vivek R, Bergsagel PL, Allred J, Greipp RP. Melphalan (M), prednisone (P) and lenalidomide (R) combination (MPR) for newly diagnosed multiple myeloma patients who are not candidates for stem cell transplantation. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 3558].
 52. Dispenzieri A, Lacy MQ, Zeldenrust SR, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. *Blood* 2007;**109**:465–70.
 53. Dispenzieri A, Lacy M, Zeldenrust S, et al. Cardiac biomarkers predict for ability to tolerate and complete therapy with lenalidomide ± dexamethasone in AL amyloidosis. *Blood (ASH Annual Meeting Abstracts)* 2006;**108**. [Abstract 130].
 54. Santhorawala V, Wright DG, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. *Blood* 2007;**109**:492–6.