March 2008 www.clinicaladvances.com Volume 6, Issue 3, Supplement 7

Recent Advances in the Use of Lenalidomide for the Treatment of Multiple Myeloma

A Review of Select Presentations
From the 49th American Society of Hematology
Annual Meeting and Exposition
December 8–11, 2007
Atlanta, Georgia

With expert commentary by:
Thierry Facon, MD
Professor
Lille University Hospital
Lille, France

Supported through an educational grant from
Celgene Corporation.

Clinical Advances in HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

Table of Contents

Recent Advances in the Use of Lenalidomide for the Treatment of Multiple Myeloma

A Review of Selected Abstracts from
the 49th Annual Meeting of the
American Society of Hematology
December 8–11, 2007
Atlanta, Georgia

Multiple myeloma, one of the most common hematologic malignancies, is characterized by a build-up of malignant plasma cells in the bone marrow, eventually resulting in anemia, lesions in the bone, and renal insufficiency. There were approximately 19,900 new cases of and 10,790 deaths due to multiple myeloma in the United States in 2007.[1]

For years the standard first-line therapy for multiple myeloma was combination therapy with an alkylating agent. This approach yields a response rate of approximately 50%, but a 5-year survival rate of just 33%.[1] Until recently the only approach to confer a survival benefit among newly diagnosed patients was chemotherapy followed by autologous stem cell transplantation (ASCT).[2,3] However, most patients are not candidates for this approach, whether due to age—the average age at diagnosis is 65 years—or comorbidities. High-dose dexamethasone has been one of the most commonly used therapies and is thought to account for approximately 85% of the effect of the VAD (vincristine, doxorubicin, dexamethasone) combination.[4-8]

The unsatisfactory outcomes with chemotherapy led to several significant therapeutic developments during the past decade. Drugs such as bortezomib (Velcade, Millennium Pharmaceuticals), a proteasome inhibitor, and the immunomodulatory agents thalidomide (Thalomid, Celgene) and lenalidomide (Revlimid, Celgene), have led to improvements in the treatment of patients with multiple myeloma. In the Assessment of Proteasome Inhibition for Extending Remissions (APEX) study, 669 patients were randomly assigned to receive either bortezomib or high-dose dexamethasone.[9] In a companion study, patients on the latter arm were permitted to cross over to bortezomib upon disease progression. In this study, patients receiving bortezomib had a higher response rate (complete response [CR] + partial response [PR]: 38% vs 18%; $P<.001$), longer median time to progression (189 vs 106 days; $P<.001$; hazard ratio [HR], 0.55), and higher 1-year survival rate (80% vs 66%; $P=.003$) compared with patients receiving high-dose dexamethasone. Grade 3 or 4 adverse events were observed in 75% of patients receiving bortezomib and 60% of patients receiving dexamethasone. This study led to the approval of bortezomib for the treatment of multiple myeloma in patients who have received at least one prior therapy.[10]

Thalidomide was the first immunomodulatory agent to be studied in multiple myeloma. Bone marrow angiogenesis is significantly increased in patients with multiple myeloma and imparts a poor prognosis.[11-13] The antiangiogenic activity of thalidomide made it a potential candidate for the treatment of this disease. A phase II study found an overall survival (OS) rate of 48% and an event-free survival rate of 20% at 24 months among 169 patients treated with thalidomide.[14] Other phase II studies of thalidomide have shown similarly encouraging results.[15-17] The combination of thalidomide plus dexamethasone also yields promising outcomes, with response rates ranging from 50% to greater than 60%.[18,19] In the first-line setting, thalidomide plus either dexamethasone or melphalan and prednisone, is associated with response rates of 58–80%.[20-23] However, thalidomide is associated with severe adverse events that greatly limit its use. In addition to its widely known teratogenic effects, dose-limiting toxicities observed in clinical trials include constipation, somnolence, and neuropathy. Forty-five percent of patients treated with thalidomide plus dexamethasone in a phase III study experienced grade 3 or higher thrombosis, rash, neuropathy, or bradycardia.[23]

Lenalidomide, an analog of thalidomide, was developed in an effort to improve on the efficacy of thalidomide while offering a better safety profile. Lenalidomide is a more potent stimulator of T cell, interleukin-2, and interferon-γ production and a more potent inhibitor of tumor

necrosis factor-α, which may lead to decreased myeloma cell growth and survival.[24-26] In addition, both of these agents inhibit the secretion of vascular endothelial growth factor, thereby reducing angiogenesis.[27]

Despite their similar mechanisms of action, lenalidomide appears to be far less toxic. Clinical trials have shown its major dose-limiting toxicity to be myelosuppression. Neurotoxicity, constipation, and somnolence occur minimally among patients treated with this immunomodulatory drug, yet its benefits equal or surpass those of thalidomide. In a phase II study comparing two dosing schedules (30 mg once daily or 15 mg twice daily) of lenalidomide, the overall response rate (ORR) among all patients was 25%, with a median duration of response of 19 and 23 months for the two dose groups, respectively.[28] Dexamethasone was added to lenalidomide for 68 of the 102 enrolled patients. The median OS among all groups was 27 months and the average progression-free survival (PFS) was 4.6 months. The most common side effects were neutropenia (61%) and thrombocytopenia (31%), both of which occurred more quickly in the twice-daily group compared with the once-daily group.

The favorable results observed with lenalidomide in phase II studies led to two identical randomized phase III trials comparing lenalidomide plus dexamethasone with dexamethasone alone in patients with refractory multiple myeloma (MM-009 in North America and MM-010 in Europe).[29,30] The studies were stopped and all patients switched to lenalidomide plus dexamethasone after an interim analysis found the experimental combination to be superior to dexamethasone alone.[31] At that time, patients receiving combination therapy showed superior OS (29.6 vs 20 months in MM-009; $P<.001$) and time to progression (TTP) (11.1 vs 5 months in MM-009 and 11.3 vs 5 months in MM-010) compared to patients receiving dexamethasone monotherapy. MM-010 reported a CR rate of 13.6% for the combination arm and 4% for the dexamethasone-alone arm.

Neuropathy, constipation, and sedation occurred in fewer than 5% of patients receiving lenalidomide. In MM-009, grade 3-4 neutropenia was observed in 36% of patients and grade 3-4 thrombocytopenia in 11%. Atrial fibrillation occurred in 5.6% of patients treated with lenalidomide, and these patients had a greater incidence of diarrhea compared with those receiving dexamethasone alone. Importantly, immunomodulatory drugs are associated with an increased risk of thromboembolic events. In MM-009, the incidence of such episodes was 5 times higher among patients receiving lenalidomide (15.3% vs 3.5%). In MM-010, the rate was lower but still significant (8.5% vs 4.5%). However, compared with thalidomide, lenalidomide appears to be a much safer and effective treatment option.

Outcomes among newly diagnosed patients have been similarly promising.[32,33] Phase III studies by the Eastern Cooperative Oncology Group (ECOG) and Southwest Oncology Group (SWOG) were initiated following the initial studies of lenalidomide in previously treated multiple myeloma. At the 2007 Annual Meeting of the American Society of Hematology, results of these and other crucial studies were presented. The following is a summary of these and other important findings pertaining to the use of lenalidomide for the first- and second-line treatment of patients with multiple myeloma. The concluding commentary by Thierry Facon, MD, of Lille University Hospital in Lille, France, underscores the significance of the latest research with lenalidomide in this setting, placing it in the broader context of the overall treatment of multiple myeloma and pointing to future research directions. The information contained in this monograph should serve as a useful update for healthcare professionals deciding courses of action for both newly diagnosed and previously treated patients with multiple myeloma.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin*. 2007;57:43-66.
2. Attal M, Harousseau J-L, Stoppa A-M, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med*. 1996;335:91-97.
3. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;348:1875-1883.
4. Kumar A, Loughran T, Alsina M, Durie BG, Djulbegovic B. Management of multiple myeloma: a systematic review and critical appraisal of published studies. *Lancet Oncol*. 2003;4:293-304.
5. Alexanian R, Barlogie B, Dixon D. High-dose glucocorticoid treatment of resistant myeloma. *Ann Intern Med*. 1986;105:8-11.
6. Friedenberg WR, Kyle RA, Knospe WH, Bennett JM, Tsiatis AA, Oken MM. High-dose dexamethasone for refractory or relapsing multiple myeloma. *Am J Hematol*. 1991;36:171-175.
7. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethasone treatment of multiple myeloma. *Blood*. 1992;80:887-890.
8. Sonneveld P, Suciu S, Weijermans P, et al. Cyclosporin A combined with vincristine, doxorubicin and dexamethasone (VAD) compared with VAD alone in patients with advanced refractory multiple myeloma: an EORTC-HOVON randomized phase III study (06914). *Br J Haematol*. 2001;115:895-902.
9. Richardson PG, Sonneveld P, Schuster MW, et al; for the Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 3005;352:2487-2498.
10. Velcade (bortezomib) for Injection. Package insert. Available at http://www.velcade.com/full_prescrib_velcade.pdf. Accessed February 19, 2008.
11. Munshi N, Wilson CS, Penn J, et al. Angiogenesis in newly diagnosed multiple myeloma: poor prognosis with increased microvessel density in bone marrow biopsies. *Blood*. 1998;92(suppl 1):98a. Abstract.
12. Vacca A, Ribatti D, Roncali L, et al. Bone marrow angiogenesis and progression in multiple myeloma. *Br J Haematol*. 1994;87:503-508.
13. Vacca A, Di Loreto M, Ribatti D, et al. Bone marrow of patients with active multiple myeloma: angiogenesis and plasma cell adhesion molecules: LFA-1, VLA-4, LAM-1, and CD44. *Am J Hematol*. 1995;50:9-14.
14. Barlogie B, Desikan R, Eddlemon P, et al. Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: Identification of prognostic factors in a phase 2 study of 169 patients. *Blood*. 2001;98:492-494.

15. Grosbois B, Belissant E, Moreau P, et al. Thalidomide in the treatment of advanced multiple myeloma: a prospective study of 120 patients. *Blood*. 2001;98:689. Abstract.
16. Kumar S, Gertz MA, Dispenzieri A, et al. Response rate, durability of response, and survival after thalidomide therapy for relapsed multiple myeloma. *Mayo Clin Proc.* 2003;78:34-39.
17. Bladé J, Esteve J, Rosinol L, et al. Thalidomide in refractory and relapsing multiple myeloma. *Semin Oncol*. 2001;28:588-592.
18. Palumbo A, Giaccone L, Bertola A, et al. Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. *Haematologica*. 2001;86:399-403.
19. Dimopoulos MA, Zervas K, Kouvatseas G, et al. Thalidomide and dexamethasone combination for refractory multiple myeloma. *Ann Oncol*. 2001;12:991-995.
20. Palumbo A, Bertola A, Musto P et al. A prospective randomized trial of oral melphalan, prednisone, thalidomide (MPT) vs oral melphalan, prednisone (MP): an interim analysis. *Blood*. 2004; 104(11): abstract 207.
21. Weber D, Rankin K, Gavino M et al. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J Clin Oncol*. 2003; 21:16-19.
22. Rajkumar SV, Hayman S, Gertz MA et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol*. 2002; 20:4319.
23. Rajkumar SV, Blood E, Vesole D et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2006; 24: 431-436.
24. Anderson KC. Lenalidomide and thalidomide: mechanisms of action – similarities and differences. *Semin Hematol*. 2005;42(4 suppl 4):S3-S8.
25. Hideshima T, Chauhan D, Shima Y, et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood*. 2000;96:2943-2950.
26. Niwayama S, Turk IS, Liu JO. Potent inhibition of tumor necrosis factor-alpha production by tetrafluorothalidomide and tetrafluorophthalimides. *J Med Chem*. 1996;39:3044-3045.
27. Gupta D, Treon SP, Shima Y, et al. Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications. *Leukemia*. 2001;15:1950-1961.
28. 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;108:3458-3464.
29. Weber DM, Chen C, Niesvizky R, et al; Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357:2133-2142.
30. Dimopoulos M, Spencer A, Attal M, et al; Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357:2123-2132.
31. Weber D. IMiDs: results of phase III studies in relapsed/refractory multiple myeloma. Virtual presentation at the 2005 American Society of Clinical Oncology Annual Meeting. Available at: http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Virtual+Meeting. Accessed February 19, 2008.
32. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood*. 2005;106:4050-4053.
33. Lacy M, Gertz M, Dispenzieri A et al. Lenalidomide plus dexamethasone (Rev/Dex) in newly diagnosed myeloma: response to therapy, time to progression, and survival. *Blood*. 2006;108: abstract 798.

Presentation Summaries

74 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[1]

SV Rajkumar, S Jacobus, N Callander, R Fonseca, D Vesole, M Williams, R Abonour, D Siegel, P Greipp

There has been much interest in exploring lenalidomide as front-line therapy for multiple myeloma. A recent Mayo clinic phase II trial of lenalidomide plus dexamethasone in 34 patients with newly diagnosed multiple myeloma showed a response rate of 91%, and a 3-year OS rate of 88%.[2] Following-up on these encouraging results, ECOG study E4A03 was initiated to compare lenalidomide in combination with high or low doses of dexamethasone as first-line induction therapy for multiple myeloma.

In this phase III study, 445 patients were randomized to one of two treatment arms, with each treatment cycle lasting 28 days. In the high-dose (HD) arm, patients received 25 mg oral lenalidomide on days 1–21, with dexamethasone administered on days 1–4, 9–12, and 17–20, for a total dexamethasone dose of 480 mg per cycle. In the low-dose (LD) arm, patients received the same dose of lenalidomide, with dexamethasone given on days 1, 8, 15, and 22, for a total dose of 160 mg per cycle.

The primary endpoint was response rate at 4 months, (ie, 4 treatment cycles). The design of the protocol was such that a difference in response rate of 15% or less met a standard for clinical equivalence. The investigators were interested in determining whether a lower versus higher dexamethasone dose leads to any difference in outcomes and adverse events in this treatment setting.

A total of 445 patients were randomized, 223 to the HD arm and 222 to the LD arm. Approximately 33% of patients had stage I disease, 41% had stage II disease, and 25% had stage III disease; over 90% of patients had an ECOG performance status <1. The average patient ages were 66 years in the HD arm and 65 years in the LD arm.

The median duration of therapy was 4 months for the HD arm and 6 months for the LD arm. In the HD arm, 43% of patients required reductions in the dose of dexamethasone and 23% required lenalidomide dose reductions; in the LD arm, 15% and 26% required dose reductions, respectively.

A total of 386 patients were evaluable for efficacy. At the primary endpoint, 2% of patients in the HD arm (n=196) had a CR and 80% had a PR, while in the LD arm (n=190) the rates were 1% and 69%, respectively. The best overall response was significantly different between the two groups (52% vs 42%, respectively; P=.06).

Survival times differed significantly between the HD and LD arms. The 12-month survival probabilities (intent-to-treat population) were 0.88 (95% confidence interval [CI], 0.83–0.92) in the HD group and 0.96 (95% CI, 0.93–0.99) in the LD group (P=.003). At 24 months the survival probabilities were 0.75 (95% CI, 0.68–0.82) and 0.87 (95% CI, 0.81–0.93), respectively (P=.009; Figure 1). The survival difference was particularly pronounced among patients age 65 years or older (Table 1).

Serious hematologic toxicities (grade 3+) included anemia (HD 8.1% and LD 6.8%), thrombocytopenia (5.4% and 5.5%), and neutropenia (11.7% and 18.7%; P=.047). Serious nonhematologic toxicities that were significantly different between the two groups were deep vein thrombosis/pulmonary embolism (DVT/PE) (HD 25% and LD 9%; P<.001), infection/pneumonia (14% and 7%; P=.030), and nonneuropathic weakness (10% and 4%; P=.008). Other serious nonhematologic toxicities were fatigue (13%, 10%), hyperglycemia (11%, 6%), cardiac ischemia (3%, 0.5%), atrial fibrillation/flutter (3%, 0.5%), and neuropathy (2%, 1.5%).

Importantly, the overall occurrence of toxicities showed a stark difference between the two treatment groups. Among 441 patient reports (222 on the HD arm and 219 on the LD arm), nonhematologic toxicities of grade 3 or higher occurred within the first four treatment cycles among 50% of patients receiving high-dose dexamethasone and 30% of patients receiving low-dose

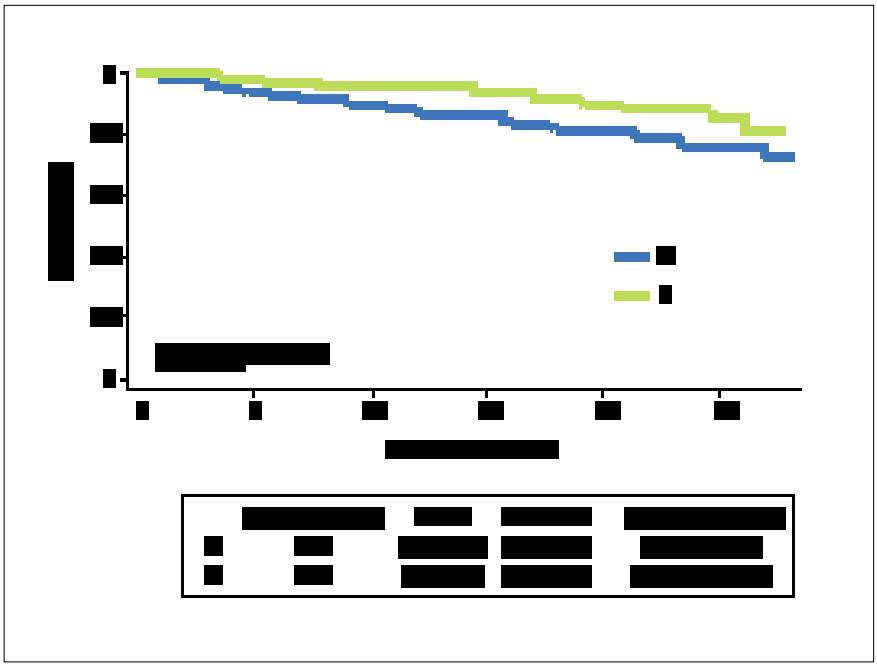

Figure 1. E4A03: Overall survival among patients treated with lenalidomide plus high-dose (Arm A) or low-dose (Arm B) dexamethasone.

Table 1. Survival Rates by Age for Patients Receiving Lenalidomide (Len) Plus High- or Low-Dose Dexamethasone

	N	12-month survival probability (95% CI)	24-month survival probability (95% CI)
Age <65:			
Len-HD	104	0.92 (0.87–0.97)	0.85 (0.78–0.93)
Len-LD	108	0.97 (0.94–1.00)	0.91 (0.84–0.98)
		P=.13*	P=.16
Age ≥65:			
Len-HD	119	0.84 (0.77–0.91)	0.67 (0.56–0.77)
Len-LD	114	0.95 (0.84–1.00)	0.82 (0.74–0.91)
		P=.01	P=.009

*P values compare high- and low-dose arms within each survival measure.

CI=confidence interval; HD=high-dose dexamethasone; LD=low-dose dexamethasone.

dexamethasone (P<.001). Throughout the entire study duration, 65% of patients on the HD arm and 45% of patients on the LD arm experienced nonhematologic toxicities of grade 3 or higher (P<.001). Grade 4 or higher toxicities of any type occurred in 19% of HD patients and 8% of LD patients (P=.001). Early deaths (<4 months on treatment) occurred in 5% and 0.5% of patients, respectively (P=.01). At a median follow-up of 21 months, 26 patients on the HD arm and 17 patients on the LD arm had died of progressive disease, and 5 patients and 1 patient, respectively, had died from thromboembolism.

In summary, this study shows that the combination of lenalidomide plus either high- or low-dose dexamethasone is active in newly diagnosed multiple myeloma. Although response rates with LD dexamethasone were comparably lower than with the HD combination, both fell within the 15% limit defined as clinically equivalent in the study design. The results show that the LD dexamethasone combination is associated with longer OS times compared with the HD dexamethasone combination. Using LD dexamethasone in combination with lenalidomide did not lead to inferior response duration, TTP, or PFS compared to the HD regimen, while the latter was associated with a greater number of myeloma- and toxicity-related deaths. These findings may have strong implications for the use of high-dose dexamethasone in the first-line treatment of multiple myeloma.

77 SWOG Protocol S0232: Dex +/– Lenalidomide for Previously Untreated Multiple Myeloma[3]

JA Zonder, JJ Crowley, MA Hussein, V Bolejack, MH Abidi, DF Moore Sr., BF Whittenberger, BGM Durie, B Barlogie

The impetus for this study stemmed from the lack of standard therapy for newly diagnosed multiple myeloma. Although several regimens are commonly used, only a small minority of patients achieve a CR and none are cured. ASCT has been found to improve CR rates and possibly survival, but clearly better regimens that improve CR and near CR (nCR) and minimize therapy-related toxicity are needed.

Several studies have found lenalidomide plus dexamethasone to be more effective than dexamethasone alone for previously treated multiple myeloma. The MM-009 (North America) and MM-010 (Europe) studies showed a significantly longer survival among patients receiving the combination versus dexamethasone alone (11.2 vs 4.7 months; *P*<.001).[4,5] A phase II study of lenalidomide plus dexamethasone found an overall response rate (ORR) of 91% among 34 patients with newly diagnosed multiple myeloma.[6]

On the basis of these findings, SWOG initiated trial S0232. Here, 198 patients were randomized to receive induction therapy with dexamethasone 40 mg on days 1–4, 9–12, and 17–20 plus either lenalidomide 25 mg daily or placebo for 28 days. The induction phase lasted for three 35-day courses. During induction therapy, all patients were required to take aspirin 325 mg/day for thromboprophylaxis.

Patients on the dexamethasone-alone arm whose disease progressed during the induction phase were allowed to cross over to the combination arm. Following induction therapy, patients on the combination arm continued with lenalidomide at a dose of 25 mg/day for 21 days plus dexamethasone at a dose of 40 mg on days 1–4 and 14–18. Patients on the dexamethasone-alone arm who did not progress during induction continued with this agent at 40 mg on days 1–4 and 14–18. Patients continued on these 28-day maintenance therapy cycles until disease progression.

Among patients receiving dexamethasone alone the CR rate was 4%, the PR rate was 49%, 38% of patients had SD, and 10% experienced progressive disease. For patients receiving lenalidomide plus dexamethasone, the CR rate was 22%, the PR rate was 62%, SD was seen in 15%, and progressive disease in 1%. The ORR (CR + PR) was significantly different between the treatment arms (84% with the combination vs 53% with dexamethasone alone; *P*=.001). Patients who crossed over from the dexamethasone arm to the combination demonstrated a CR rate of 15% and a PR rate of 55%.

Progression-free survival was also significantly different, with 12-month estimates of 77% with combination treatment and 55% with dexamethasone alone (*P*=.002; Figure 2). OS was similar between the two groups (93% vs 91% at 12 months, respectively). Among patients who crossed over from the single-drug arm to the combination, the 1-year OS and PFS rates were 72% and 62%, respectively.

The incidence of grade 3/4 neutropenia was statistically significantly different between the combination and dexamethasone-alone arms (13.8% vs 2.4%, respectively; *P*=.010), as was the occurrence of infections (all grades: 51.4% vs 28%; *P*=.003). Grade 3–5 infections occurred in 18.9% and 9.8% of patients, respectively (not a statistically significant difference), with 1 death on the combination arm. Other major adverse events included grade 3/4 thrombocytopenia (4.2% vs 2.4%), grade 3/4 anemia (8.3% vs 9.8%), hyperglycemia (all grades, 51.4% vs 57.3%), and depression (all grades, 33.3% vs 20.7%). Thromboembolic events were observed in 25 patients receiving lenalidomide plus dexamethasone and 7 patients receiving dexamethasone alone (*P*=.089).

In summary, the SWOG S0232 trial showed that the combination of lenalidomide plus dexamethasone is more active than dexamethasone alone in newly diagnosed multiple myeloma in terms of ORR, CR, and OS. Some major toxicities were more common with the combination, but these were largely manageable. Thromboembolism rates were high even while patients were taking aspirin, although levels of compliance and other risk factors are unknown. The investigators posited that lowering the dexamethasone dose might lower the incidence of blood clots.

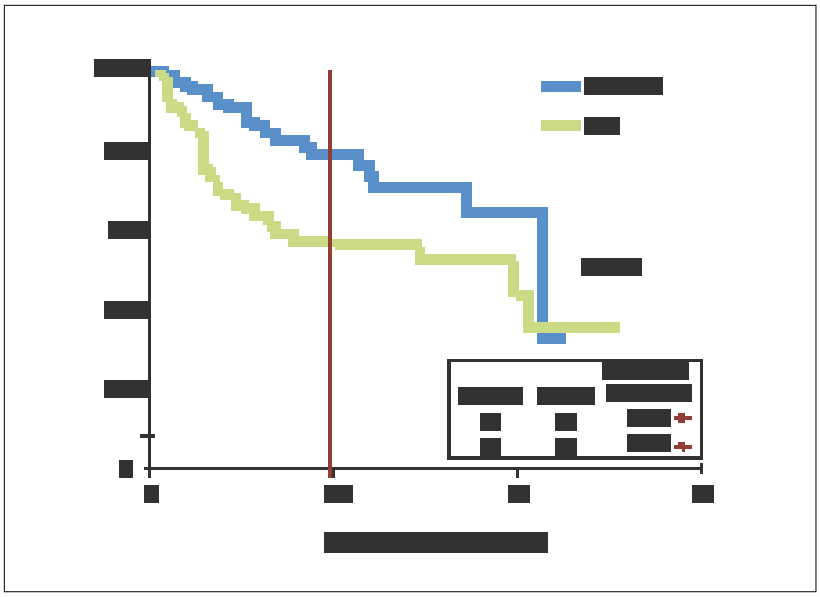

Figure 2. S0232: progression-free survival among patients treated with lenalidomide/dexamethasone versus dexamethasone alone.

187 An Open-Label Phase I/II Study of the Safety and Efficacy of Bortezomib, Lenalidomide, and Dexamethasone Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma[7]

P Richardson, S Jagannath, N Raje, A Jakubowiak, S Lonial, D Avigan, I Ghobrial, R Schlossman, A Mazumder, N Munshi, R Joyce, D Doss, D Warren, S Hayes, L Giove, S Kaster, C Delaney, M Lauria, C Mitsiades, T Hideshima, R Knight, D-L Esseltine, K Anderson

Phase III studies have confirmed that both bortezomib and the combination of lenalidomide plus dexamethasone produce superior outcomes among patients with previously treated multiple myeloma compared to dexamethasone alone.[4,5,8-11] In addition, the combinations of bortezomib plus dexamethasone and lenalidomide plus dexamethasone have both proven active in newly diagnosed multiple myeloma.[2,6,12,13] Mitsiades and colleagues have reported preclinical evidence of synergy between lenalidomide and bortezomib.[14]

A phase I study reported at the 2006 ASH annual meeting found that lenalidomide plus bortezomib was well tolerated and active among 38 patients with relapsed/refractory multiple myeloma. The study also identified a maximum tolerated dose (MTD) of 15 mg for lenalidomide and 1.0 mg/m^2 for bortezomib.[15]

Building on these studies, Richardson and colleagues initiated a phase I/II study to define the MTD of the triple combination of lenalidomide, bortezomib, and dexamethasone and determine the response rate of this regimen among newly diagnosed multiple myeloma patients. Secondary objectives included identifying the CR and PR rates after 4 and 8 cycles, the combined CR plus nCR rate, measuring duration of response and survival, assessing toxicity, and finding surrogate markers that might better define the mechanisms of action. For patients proceeding to ASCT after treatment, stem cell harvesting data were obtained and engraftment parameters were defined.

A total of 53 patients (median age 58 years; range 22–86) with newly diagnosed multiple myeloma were enrolled. Patients received lenalidomide on days 1–14 of a 21-day cycle, for up to 8 cycles. Bortezomib was given on days 1, 4, 8, and 11, and dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12. Patients who achieved a PR or better were permitted to proceed to ASCT beginning at cycle 4. Patients with at least SD were given maintenance therapy with bortezomib once weekly plus dexamethasone on days 1, 2, 8, and 9. Accompanying prophylactic therapy included daily aspirin to prevent thromboembolism and antiviral therapy to prevent herpes zoster.

In phase I, intended to identify the MTD, patients were enrolled in cohorts of 3–6 patients, with each cohort assigned to a dose level as shown in Table 2. The MTD was defined as the dose level prior to that resulting in two or more dose-limiting toxicities. Dose-limiting toxicities

Table 2. Phase I Dose Levels

Dose level*	Lenalidomide	Bortezomib	Dex†	Pts (N=33)
1	15 mg/d	1.0 mg/m^2	40 mg	3
2	15 mg/d	1.3 mg/m^2	40 mg	3
3	20 mg/d	1.3 mg/m^2	40 mg	4‡
4	25 mg/d	1.3 mg/m^2	40 mg	6
4M§	25 mg/d	1.3 mg/m^2	20 mg	17

*As of 12/1/07. An additional dose level, 4M, was introduced based on safety data.

†20 mg, cycles 5–8.

‡1 patient in each never received treatment; not included in maximum tolerated dose determination.

§Starting dexamethasone dose changed to 20 mg/day as patient safety data beyond cycle 1 indicated 40 mg/day dose was not well tolerated.

included grade 3 or higher nonhematologic toxicity, grade 4 thrombocytopenia with platelets less than 10,000/m^3 on more than one occasion despite transfusion support, grade 4 neutropenia for more than 5 days and/or febrile neutropenia, or an inability to receive treatment on day 1 of cycle 2 due to drug-related toxicity. Following identification of the MTD, an additional 10 patients were enrolled.

The investigators assessed toxicity according to NCI-CTC v3.0. Responses were assessed using both European Group for Blood and Marrow Transplant (EBMT) criteria and International Uniform Response Criteria, modified to include nCR.[16,17] Per EBMT criteria, responses among evaluable patients were confirmed twice, 6 weeks apart.

In the phase I study, 2 patients experienced dose-limiting grade 3 hyperglycemia due to dexamethasone (40 mg dose). The maximum planned doses of lenalidomide 25 mg, bortezomib 1.3 mg/m^2, and dexamethasone 20 mg were reached. At the time this study was presented at ASH, phase I enrollment was completed and phase II enrollment was ongoing at the MTD.

At the 2007 ASH annual meeting, the investigators presented a summary of treatment given to date in phases I and II. Sixteen patients had completed 8 or more cycles and 7 had proceeded to stem cell collection. Fourteen patients had discontinued the trial due to transplant (n=5), patient preference (n=3), progressive disease (n=2), underlying renal disease (n=1), death unrelated to treatment (n=1), neuropathic pain (n=1), and DVT (n=1). Eighteen patients (15 of whom were in dose levels 1–4 as specified in Table 2) required dexamethasone dose reductions, 12 required lenalidomide dose reductions (8 in levels 1–4), and 11 required bortezomib dose reductions (8 in dose levels 1–4).

The most common grade 3/4 toxicities were metabolic-related adverse events, thrombocytopenia, neutropenia, infection, liver problems, and pneumonia. There have been no incidents of treatment-related mortality, and the investigators reported that no unexpected toxicities have occurred.

Among 42 evaluable patients, CR was seen in 9 patients, nCR in 3, PR in 29, VGPR in 10, and minor response in 1; all responses are awaiting confirmation. The ORR—CR, nCR, and PR combined—was 98% (95% CI, 87.4–99.9%). More specifically, the combined CR plus nCR rate was 29%, and the rate of CRs, nCRs, and VGPRs together was 52%. Table 3 shows all responses according to phase and dose level.

Table 3. Responses According to Phase and Dose Cohort

Dose level	Response-evaluable pts, n	CR	nCR	VGPR	PR	MR
Phase I	31	8 (26%)	3 (10%)	9 (29%)	10 (32%)	1 (3%)
1	3	1	1		1	
2	3	2		1		
3	3	1			2	
4	6	1		3	2	
4M	16	3	2	5	5	1
Phase II	11	1 (9%)		1 (9%)	9 (82%)	
Total	42	9 (21%)	3 (7%)	10 (24%)	19 (45%)	1 (2%)

At the time of this presentation, for patients with confirmed response, the median duration of response was 5 treatment cycles (range 2–11).

CR=complete response; MR=minor response; nCR=nodal CR; PR=partial response; VGPR=very good PR.

At a median follow-up of 4 months, the median TTP, PFS, and OS had not been reached. Regarding ASCT, a median of 11.51 × 10^6 CD34(+) cells had been collected after a median of 6 cycles of therapy, and engraftment data were pending.

At the presentation of this analysis, the authors concluded that the combination of bortezomib, lenalidomide, and dexamethasone is active in newly diagnosed multiple myeloma patients, with manageable toxicities and no adverse effect on stem cell harvesting. Enrollment in phase II is ongoing, with plans for additional analyses of cytogenetics, proteomics, and gene expression profiling.

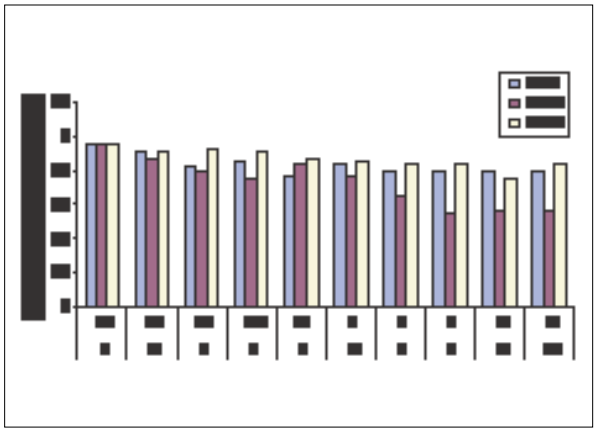

Figure 3. Dose reductions required for lenalidomide (Len), cyclophosphamide (CTX), and dexamethasone (Dex).

190 Phase 2 Trial of Lenalidomide, Cyclophosphamide, and Dexamethasone for Newly Diagnosed Myeloma[18]

SK Kumar SR, Hayman, FK Buadi, MQ Lacy, PR Greipp, SJ Russell, SR Zeldenrust, MA Gertz, K Stewart, L Bergsagel, R Fonseca, J Allred, M Campbell, JA Lust, TE Witzig, SV Rajkumar, A Dispenzieri

Based on the documented activity of lenalidomide plus dexamethasone in newly diagnosed multiple myeloma, the efficacy of alkylating agents in the treatment of multiple myeloma, and the inclusion of cyclophosphamide in first-line treatment regimens for this disease,[2,19,20] Kumar and colleagues initiated a phase II study to examine the addition of an alkylating agent to the combination of lenalidomide plus dexamethasone. A total of 33 patients (median age 63 years; range 44–79) received lenalidomide 25 mg on days 1–21, cyclophosphamide 300 mg/m^2 on days 1, 8, and 15, and dexamethasone 40 mg on days 1, 8, 15, and 22 in 28-day cycles. Patients received this treatment for 4 cycles or until disease progression. In addition, all patients received either aspirin or full anticoagulation. After 4 cycles, responding patients or those with SD either continued until disease progression or underwent transplantation. Other patients continued to be monitored. The primary endpoint was response at 4 cycles.

As of the time of presentation, 4 patients had ended treatment before 4 cycles and 3 patients had not yet received 4 cycles; 13 patients were still on study after a median of 6 cycles (range, 3–14). At a median follow-up of 7 months (range, 2.8–15.2 months) with 31 patients, 19% achieved a VGPR/nCR, 65% achieved a PR, and 16% had SD or a minor response. PD was observed in 6 patients, 3 of whom were still enrolled in the study, 2 of whom had completed 4 cycles of therapy, and 1 of whom had discontinued treatment due to an adverse event.

Among 33 patients, grade 3/4 hematologic toxicities were observed in 60% of patients, and grade 3/4 nonhematologic toxicities in 63%. Grade 3/4 hematologic toxicities included leukopenia (12%), neutropenia (48%) and thrombocytopenia (15%). The most common grade 3/4 nonhematologic toxicities were fatigue (15%), thromboembolism (21%), infection (15%), and neurological problems (24%).

Of the three drugs, dose reductions were most often necessary for cyclophosphamide over the course of 10 cycles of therapy (Figure 3). Twenty patients discontinued study therapy due to toxicity (n=3), disease progression (n=3), protocol completion (n=13), or preference for an alternative treatment (n=1). A total of 15 patients have proceeded to stem cell collection after four or more treatment cycles, with an average collection of 8.5 × 10^6 CD34(+) cells/kg. Four patients have since undergone ASCT.

The study authors concluded that the triple combination of lenalidomide, cyclophosphamide, and dexamethasone is active in newly diagnosed multiple myeloma, and recommend expanding the trial with a reduced cyclophosphamide dose. They also suggested a two-arm study to compare this regimen with others in the first-line setting.

Table 4. Patient Characteristics from MM-009 and MM-010

	Len/Dex	Dex
Number of patients	353	351
Male, %	60	59
Median age, yr	63	63
ECOG PS <1, %	87	89
Mean years from initial therapy	3.2	3.4
Two or more prior treatments	82	79
Prior thalidomide, %	36	42
Durie–Salmon stage III, %	65	64
Lytic lesions, %	73	78
Mean marrow plasmacytosis, %	35	31

ECOG=Eastern Cooperative Oncology Group; PS=performance status.

412 Prolonged Overall Survival With Lenalidomide Plus Dexamethasone Compared With Dexamethasone Alone in Patients With Relapsed or Refractory Multiple Myeloma[21]

D Weber, R Knight, C Chen, A Spencer, Z Yu, J Zeldis, M Olesnyckyj, M Dimopoulos, on Behalf of the MM-009 and MM-010 Investigators

As discussed above, lenalidomide is an oral immunomodulator with antiangiogenic and apoptotic properties.[22] This agent, a derivative of thalidomide, has been designed to be more effective and less toxic than its predecessor.

Two identical phase III clinical trials were conducted at 48 centers in the US and Canada (MM-009) and 51 centers across Europe, Australia, and Israel (MM-010) comparing lenalidomide plus dexamethasone with dexamethasone alone in patients with relapsed or refractory multiple myeloma. Patients were required to have had no more than three prior therapies, no resistance to dexamethasone, creatinine <2.5 mg/dL, and normal hepatic function. Prior to randomization, patients were separated according to β2-microglobulin level (<2.5 vs ≥2.5 mg/L), number of prior transplants (0 vs ≥1), and number of prior multiple myeloma treatments (1 vs ≥2). Patients were randomly assigned to receive 25 mg of oral lenalidomide or placebo on days 1–21 of a 28-day cycle. In addition, all patients received 40 mg of oral dexamethasone on days 1–4, 9–12, and 17–20 for the first four cycles; for subsequent cycles they received dexamethasone only on days 1–4. Patients continued in the study until the occurrence of disease progression or unacceptable toxic effects. Safety, clinical response, TTP, and OS were assessed.

A planned interim analysis was scheduled once 50% of patients (n=111) had progressed. For MM-009, patients were enrolled from February 2003 to May 2004, with 50% of patients having progressed by July 2004. MM-010 enrolled patients from September 2003 to September 2004, at which time 50% of patients had progressed.

A combined total of 704 patients were randomized, 353 to the combination arm and 351 to the dexamethasone-only arm. The median age of patients was 63 on both arms; other patient characteristics are detailed in Table 4. Most patients (73% on the combination arm and 70% on the dexamethasone-only arm) had received prior treatment with dexamethasone, and 58% of patients on each arm had previously undergone stem cell transplantation. Other prior therapies included thalidomide for 36% and 42% of patients, respectively, and bortezomib for 8% of patients on each arm.

The analysis presented at the 2007 ASH meeting pooled patients from both MM-009 and MM-010. Responses were measured according to EBMT criteria.[16] The PR rate was 61% among patients receiving lenalidomide plus dexamethasone and 23% among patients receiving dexamethasone alone (P<.001). CR rates were 15% and 2%, respectively, and nCR rates were 9% and 1.4%, respectively.

The combination arm proved advantageous in terms of both disease progression and survival times. The median TTP was 11.2 for patients receiving lenalidomide plus dexamethasone and 4.7 months for patients receiving dexamethasone alone (P<.001). The median OS was 35 and 31 months, respectively (P=.015). The investigators noted that lenalidomide plus dexamethasone was associated with a continued survival benefit even after 47% of patients from the control arm had crossed over to the combination treatment (Figure 4).

The investigators presented several interesting analyses of the TTP data. Broken out by age group, the difference between the treatment arms remained apparent: for patients under age 65 the median TTP was 11.2 months and 4.7 months for the combination and dexamethasone-alone arms, respectively; for patients aged 65–75 years it was 13.3 and 4.7 months, respectively; and for patients over age 75 years it was 13.3 and 4.7 months, respectively. Interestingly, for the combination treatment group, the median TTP was longer among patients who had received just one prior therapy compared with those who had

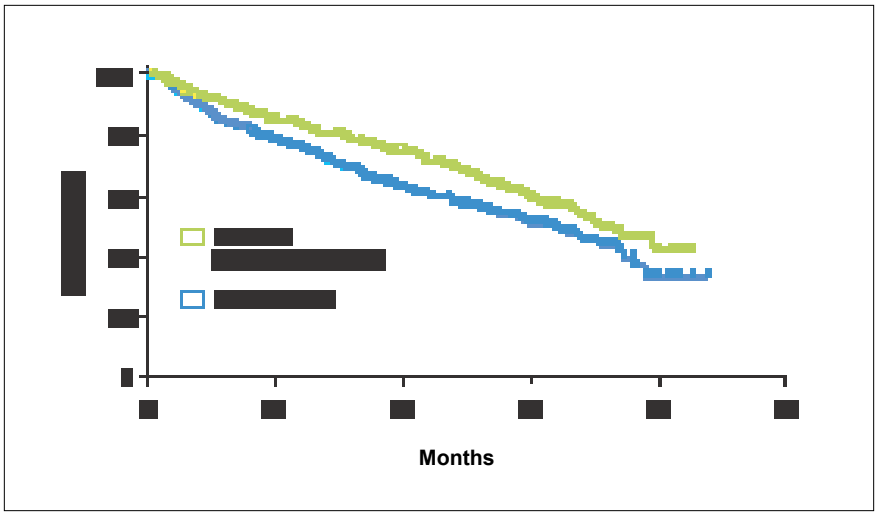

Figure 4. Overall survival among patients treated with lenalidomide + dexamethasone (Len/Dex) versus dexamethasone (Dex) + placebo. Survival benefit retained despite 47% crossover from Dex to Len/Dex.

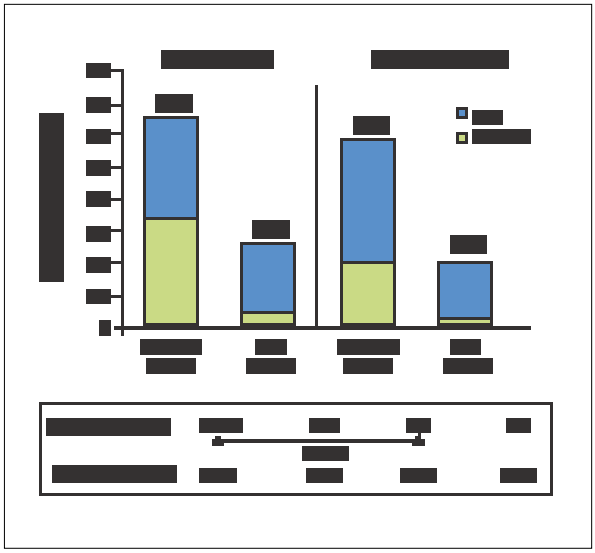

Figure 5. Response and TTP at first relapse among patients treated with lenalidomide + dexamethasone (Len/Dex) versus dexamethasone plus placebo (Dex).

CR=complete response; nCR=nodal CR; OS=overall survival; PR=partial response; TTP=time to progression.

received two or more (14.5 vs 9.6 months, respectively; *P*<.05; Figure 5). Overall survival also differed between these subgroups (39.1 vs 33.3 months, respectively), although it was not statistically significant.

Among patients receiving the combination treatment, the most common grade 3 or 4 adverse events were DVT and PE, thrombocytopenia, anemia, and neutropenia.

Table 5. Thrombosis and Concomitant Erythropoietin (EPO) or Aspirin (ASA)

	Thrombotic episodes					
	Len/Dex			Dex		
	(n=353)	%	*P*	(n=353)	%	*P*
No-EPO	25/217	12	.33	6/245	2	.04
EPO	21/136	15		8/105	8	
No-ASA*	46/345	13	.60	16/335	5	1.0
ASA*	0/8	0		0/15	0	

* Prophylactic aspirin use in the first month of therapy.

The most common adverse events, grades 1–4, among patients receiving dexamethasone alone were fatigue, diarrhea, nausea, constipation, and anemia. Of note on the combination arm, myelosuppression was more pronounced among patients who had undergone stem cell transplantation and those with severe renal impairment.

The occurrence of thrombosis was analyzed in light of whether patients had received concomitant erythropoietin or aspirin. As with studies discussed above, the benefit of aspirin remains unclear, with no statistically significant difference in the occurrence of thrombosis seen between patients who were taking aspirin and those who were not (Table 5).

The reasons for discontinuation presented in this interim analysis reveal interesting differences between the two treatment arms. Among 353 patients who received lenalidomide plus dexamethasone, 41% discontinued

therapy because of progressive disease and 17% because of adverse events. By comparison, 71% of dexamethasone-alone patients discontinued because of progressive disease and 9% because of adverse events.

In summary, this combined interim analysis of MM-009 and MM-010 found that the combination of lenalidomide plus dexamethasone extended OS compared with dexamethasone alone in patients with relapsed/refractory multiple myeloma. Response rates and TTP were likewise increased with the combination. Myelosuppression and thrombotic events occurred more often with the combination treatment. Separate analyses of MM-009 and MM-010 have been reported in the *New England Journal of Medicine*.[4,5]

3024 Cyclophosphamide Overcomes the Suppressive Effect of Lenalidomide Therapy on Stem Cell Collection in Preparation for Autologous Stem Cell Transplantation for Multiple Myeloma[23]

T Mark, D Jayablan, RN Pearse, J Stern, JB Furst, F Zafar, A LaRow, RN Pearse, J Harpel, T Shore, MW Schuster, JP Leonard, PJ Christos, M Coleman, R Niesvizky

With new treatment regimens yielding high response rates in patients with multiple myeloma, there has been a recent trend toward delaying ASCT until relapse. However, ASCT following high-dose chemotherapy is associated with prolonged survival and remains a primary treatment goal. Thus, there is an interest in determining how a potential induction therapy affects stem cell collection. Also, with studies showing a survival benefit from tandem ASCTs, the number of stem cells required for transplantation has increased.[24-26]

Lenalidomide plus dexamethasone has demonstrated activity in the treatment of both newly diagnosed and previously treated multiple myeloma. However, two studies have also found a decreased stem cell yield with stem cell mobilization by granulocyte colony-stimulating factor (G-CSF) following lenalidomide induction therapy.[24] One of these studies found lower stem cell yield to correlate with the duration of lenalidomide therapy, leading the authors to recommend collection within 6 months of lenalidomide initiation. This correlation was not corroborated in the other report (Mazumder A, personal communication).

In the present study, Mark and colleagues explored whether adding cyclophosphamide to G-CSF as a mobilization regimen would improve the ability to collect adequate yields of stem cells for at least two ASCTs among patients who had undergone induction therapy with the BiRD regimen (clarithromycin/lenalidomide/dexamethasone).

Twenty-nine patients with newly diagnosed multiple myeloma (Durie-Salmon stage II or III) were enrolled in this study. BiRD therapy, given to all patients, consisted of clarithromycin 500 mg orally twice daily on days 1–28, lenalidomide 25 mg orally on days 1–21, and dexamethasone 40 mg orally on days 1, 8, 15, and 21. Stem cell collection was performed after patients achieved maximum disease response or disease plateau, with BiRD withheld for at least 14 days prior to mobilization.

Stem cell mobilization therapy consisted of either G-CSF alone (10 mcg/kg per day for 5–10 days until 10×10^6/kg CD34(+) stem cells had been collected or G-CSF plus cyclophosphamide given at a dose of 3 g/m^2 once before G-CSF.

Measures compared between the two groups included the number of CD34(+) cells collected, the ability to collect enough stem cells for two ASCTs, and the impact of BiRD treatment duration on this yield. Baseline characteristics were similar among all patients. Nine patients received G-CSF alone, 20 patients received G-CSF plus cyclophosphamide, and 1 patient received both pre-collection regimens.

The investigators reported that significantly more CD34(+) cells were collected from patients who received both cyclophosphamide and G-CSF compared with those who received G-CSF alone (median 14.2×10^6/kg vs 3.1×10^6/kg; $P<.0001$) (Table 6). Enough cells for two ASCTs were obtained from all patients who received the combination versus 33% of those who received G-CSF alone. The number of BiRD therapy cycles did not correlate with stem cell harvest success (median 7.0 cycles [range, 2–27] and 7.5 cycles [range, 7–23] for successful and unsuccessful harvests, respectively), or with the amount of CD34(+) cells collected.

The investigators drew several conclusions from this study. First, the results provide a strong rationale for the addition of cyclophosphamide to G-CSF for stem cell mobilization following BiRD therapy. Second, the number of BiRD treatment cycles does not appear to be a limiting factor with regard to stem cell collection. Finally, G-CSF plus cyclophosphamide following BiRD therapy enables harvesting of enough CD34(+) stem cells

Table 6. Stem Cell Mobilization with G-CSF Alone vs CTX Plus G-CSF Following BiRD Therapy

	G-CSF (n=9)	CTX plus G-CSF (n=20)	*P*
CD34+ collection, × 10^6/kg			
Mean (SD)	3.8 (3.3)	32.3 (51.1)	.0001*
Median (range)	3.1 (0.2–8.6)	14.2 (4.9–236.3)	.0001*
Successful yield, n (%)	3 (33)	20 (100)	.0001†

*Mann-Whitney U test.

†Fisher's exact test.

BiRD=clarithromycin/lenalidomide/dexemethasone; CTX=cyclophosphamide; G-CSF=granulocyte colony-stimulating factor; SD=standard deviation.

for two ASCTs. In summary, the study authors recommended that lenalidomide-based therapy for multiple myeloma be continued until the desired tumor reduction has been achieved, and that the combination of G-CSF and cyclophosphamide effectively mobilizes stem cells prior to ASCT.

3597 Lenalidomide Overcomes Poor Prognosis Conferred by del(13q) and t(4;14) in Multiple Myeloma: Results of the Canadian MM016 Trial[27]

NJ Bahlis, K Song, Y Trieu, B Roland, E Masih-Khan, H Chang, H Bruyere, A Mansoor, D Horsman, M Eliaswiz, D Stewart, D Reece

Multiple myeloma patients with genomic aberrations such as t(4;14) and del(17p13) have been shown to have poorer responses and survival times compared to patients without these genetic abnormalities.[28] Since the combination of lenalidomide and dexamethasone has demonstrated superior activity and survival among patients with previously treated multiple myeloma compared with dexamethasone alone, it is of interest to see whether this benefit still holds among the subgroup of patients with genomic aberrations associated with poor prognosis.[4,5,10,11]

MM-016 is a single-arm, open-label, multicenter expanded access program for patients with previously treated multiple myeloma. A total of 120 patients were given lenalidomide 25 mg/day orally on days 1–21 of a 28-day cycle, plus pulse dexamethasone. The presence or absence of del(13), t(4;14), and del(17p13) were identified using commercial fluorescent in situ hybridization probes. In evaluating the data, patients with t(4;14) or del(17p13) abnormalities were considered to have high-risk disease. Responses were evaluating according to EBMT/IBMTR criteria.[16]

The median age of the patients enrolled in this study was 61 years (range, 32–79). Previous treatments included thalidomide (57.5%), bortezomib (49.2%), and stem cell transplantation (68.3%), with 58.3% of patients having had three or more prior therapies. Most patients had International Staging System (ISS) stage I or II disease (34.2% and 36.7%, respectively), 18.3% had stage III disease, and disease stage data were missing for 10.8% of patients.

The data were evaluated in several analyses. First, responses were analyzed according to the various genomic aberration subgroups. Statistically significant differences in response were noted among patients with versus without del(17p13) but not among patients with versus without t(14;4) or del(14) (Table 7).

The 12-month risks of progression and mortality were also compared among various patient subgroups (Table 8). According to this analysis, there was no significant difference in either measure between patients with or without del(13q), t(4;14), or del(17p13).

The investigators also looked at factors associated with disease progression using a Cox proportional-hazards regression analysis. The factors analyzed included the presence of a high-risk aberration, ISS stage, types of prior therapy, and number of prior therapies. According to the analysis, only prior thalidomide treatment was associated with a higher risk of disease progression among the patients enrolled in this study (HR, 2.2; 95% CI,1.3–3.7; *P*=.003).

Based on these analyses, the authors concluded that multiple myeloma patients with t(4;14) and/or del(17p13) mutations did not fare worse than patients without these aberrations when treated with lenalidomide plus dexamethasone. Prior treatment with thalidomide was the only factor that appeared to be associated with a higher risk of disease progression. Patients with del(17p13) did show some signs of poorer outcomes, but the differences were not statistically significant.

Table 7. Response Rates According to Patient Subgroup*

Subgroup	CR + nCR, %	PR, %	MR, %	
All patients	10.8	63.3	11.7	
del(13)	6.7	60	13.3	
No del(13)	14.1	64.8	9.9	
t(4;14)	9.1	63.7	13.6	
No t(4;14)	11.2	65.2	10.1	
del(17p13)	-	63.6	9.1	
No del(17p13)	12.9	60	11.8	*P*<.05
Prior thalidomide	8.7	59.4	14.5	
No prior thalidomide	13.8	68.6	7.8	*P*<.05
Prior bortezomib	12.1	62	6.9	
No prior bortezomib	9.8	65.6	14.8	

**P*>.05 for subgroup comparisons except where indicated.

CR=complete response; nCR=near CR; PR=partial response; MR=minor response.

3598 Relapsed/Refractory Multiple Myeloma Patients Treated With Lenalidomide/Dexamethasone Who Achieve a Complete or Very Good Partial Response Have Longer Time to Progression Compared With Patients Achieving a Partial Response[29]

J-L Harousseau, DM Weber, M Dimopoulos, M Olesnyckyj, Z Yu, JB Zeldis, RD Knight, D Siegel

In the MM-009/010 studies discussed above, patients with relapsed/refractory myeloma treated with lenalidomide plus dexamethasone had superior outcomes to patients who received dexamethasone alone.[4,5,21] Previous experience has shown that patients who achieve a CR following chemotherapy and ASCT are more likely to have a favorable long-term survival.[30,31] The benefit of achieving a CR following high-dose therapy has been demonstrated in newly diagnosed multiple myeloma, but until now the numbers of patients with previously treated disease achieving CRs have been too small to show any significant differences in survival compared with patients achieving other responses.

The MM-009/010 data present an opportunity to examine the prognostic value of CRs and VGPRs compared with PRs in previously treated multiple myeloma. Harousseau and colleagues conducted a subanalysis of these data in order to determine whether achieving a CR or VGPR was associated with prolonged survival and TTP compared with achieving a PR following treatment with lenalidomide plus dexamethasone.

Data from the combination arms of the MM-009 and MM-010 studies were pooled and responses were assessed according to the International Uniform Response Criteria.[17] Patients were divided into two groups based on response (CR/VGPR [n=114] or PR [n=100]) and between-group differences in TTP, response duration, time to response, OS, and adverse events were assessed. Disease stage and performance status were similar between the groups. The median age of patients was 64 years (range, 33–86) in the CR/VGPR group and 62 years (range, 25–84) in the PR group. The median time since diagnosis was 2.8 years (range, 0.5–14.6) versus 3.6 years (range, 0.4–14.2), respectively. More patients in the CR/VGPR group had undergone just one prior therapy (42% vs 33%, respectively), and fewer had undergone two prior therapies (58% vs 67%, respectively).

Distribution of response over time is shown in Figure 6. Among the patients that achieved a CR/VGPR, 46% started as partial responders and improved with additional treatment cycles, with 16% of the CR/VGPRs occurring after cycle 10. Patients who achieved CRs/

Table 8. Lenalidomide + Dexamethasone for Previously Treated Multiple Myeloma: Progression and Mortality Risks by Patient Subgroup

	n	12-mo risk of progression, %	*P*	12-mo risk of mortality, %	*P*
All patients	120	67.8	-	39.7	-
High-risk	31	72.9	.35	38.7	.96
Low-risk	89	66.2		40	
del(13q)	74	67.9	.63	40.8	.70
No del(13q)	46	67.5		39	
t(4;14)	22	69	.96	27.9	.38
No t(4;14)	89	68.3		40	
del(11p13)	11	75.8	.16	63.6	.09
No del(17p13)	95	65.6		39.2	

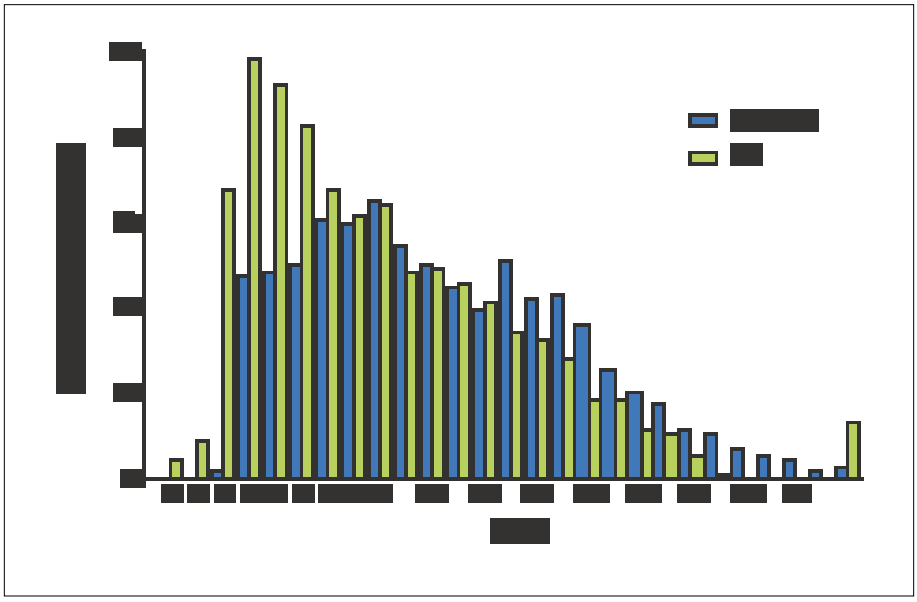

Figure 6. Distribution of response to lenalidomide/dexamethasone by treatment cycle.

CR=complete response; PR=partial response; VGPR=very good PR.

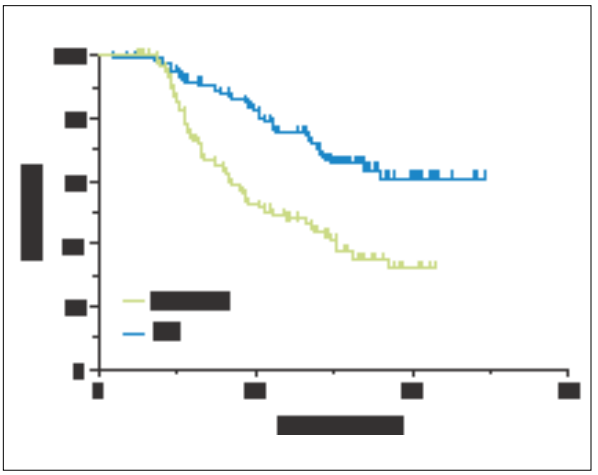

Figure 7. MM-009/010 subanalysis: Kaplan-Meier plots of time to progression (TTP) in patients treated with lenalidomide plus dexamethasone (intent-to-treat population).

CR=complete response; PR=partial response; VGPR=very good PR.

VGPRs sustained those responses longer than those who achieved PRs (median not reached for CR/VGPR vs 38 weeks for PR; HR 2.56; *P*<.001). The median TTP was also significantly longer among the CR/VGPR group compared with the PR group (median not reached for CR/VGPR vs 48.1 weeks for PR; HR, 2.43; *P*<.001) (Figure 7). Median OS was similar between the CR/VGPR (trending toward an advantage) and PR groups (median not reached for either group; HR, 1.29 [in favor of CR]; *P*=.294). Finally, the mean duration of treatment was statistically significantly longer for the CR/VGPR group versus the PR group (68.3 vs 53.3 weeks; *P*<.001).

Adverse events were similar between the two groups, with at least one occurrence of a grade 3 or higher event seen among 86% of patients in the CR/VGPR group and 84% of patients in the PR group. The most common grade 3 or higher adverse events were neutropenia (40% and 44%, respectively) and thrombocytopenia (13% and 16%, respectively).

The investigators drew several conclusions from this analysis of the MM-009/010 data. First, patients with relapsed/refractory multiple myeloma treated with lenalidomide/dexamethasone who achieved a CR/VGPR showed a longer response duration and longer TTP compared with those who achieved PRs, an effect that persisted regardless of the number of previous therapies. CR/VGPR was also associated with a nonsignificant trend toward longer OS. Also noteworthy was the finding that maintaining patients on this combination therapy often resulted in late-occurring CRs and VGPRs, an observation that the authors thought warranted further investigation.

References

1. Rajkumar SV, Jacobus S, Callander N, et al. 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. Presented at the 49th Annual Meeting and Exposition of the American Society of Hematology. December 8–11, 2007; Atlanta, GA.
2. 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;82:1179-1184.
3. Zonder JA, Crowley J, Hussein M, et al. SWOG protocol S0232: dex +/- lenalidomide for previously untreated myeloma. Presented at the 49th Annual Meeting and Exposition of the American Society of Hematology. December 8–11, 2007; Atlanta, GA.
4. Weber DM, Chen C, Niesvizky R, et al; Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357:2133-3142.
5. Dimopoulos M, Spencer A, Attal M, et al; Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357:2123-2132.
6. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood*. 2005;106:4050-4053.
7. Richardson P, Jagannath S, Raje N, et al. An open-label phase I/II study of the safety and efficacy of bortezomib, lenalidomide, and dexamethasone combination therapy for patients with newly diagnosed multiple myeloma. Presented at the 49th Annual Meeting and Exposition of the American Society of Hematology. December 8–11, 2007; Atlanta, GA.
8. Richardson PG, Sonneveld P, Schuster MW, et al; Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;352:2487-2498.
9. Richardson PG, Sonneveld P, Schuster, M, eta l. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood*. 2007;110:3557-3560.
10. Dimopoulos MA, Spencer A, Attal M, et al. Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): results of a phase 3 study (MM-010). *Blood* (ASH Annual Meeting Abstracts). 2005;106: Abstract 6.
11. 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;108:3458-3464.
12. Harousseau JL, Attal M, Leleu X, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. *Haematologica*. 2006;91:1498-1505.
13. Jagannath S, Durie BGM, Wolf JL, et al. Long-term follow-up of patients treated with bortezomib alone and in combination with dexamethasone as frontline therapy for multiple myeloma. *Blood* (ASH Annual Meeting Abstracts). 2006;108: Abstract 796.
14. Mitsiades N, Mitsiades CS, Poulaki V, et al. Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. *Blood*. 2002;99:4525-4530.
15. 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.
16. Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol*. 1998;102:1115-1123.
17. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response *criteria for multiple myeloma. Leukemia. 2006;20:1467-1473.*

18. Kumar SR, Hayman SR, Buadi FK et al. Phase 2 trial of lenalidomide, cyclophosphamide, and dexamethasone for newly diagnosed myeloma. Presented at the 49th Annual Meeting and Exposition of the American Society of Hematology. December 8–11, 2007; Atlanta, GA.
19. Lenhard RE Jr, Oken MM, Barnes JM, Humphrey RL, Glick JH, Silverstein MN. High-dose cyclophosphamide. An effective treatment for advanced refractory multiple myeloma. *Cancer*. 1984;53:1456-1460.
20. Case DC Jr, Sonneborn HL, Paul SD, et al. Combination chemotherapy for multiple myeloma with BCNU, cyclophosphamide, vincristine, melphalan, and prednisone (M-2 protocol). *Oncology*. 1985;42:137-140.
21. Weber D, Knight R, Chen C, et al. Prolonged overall survival with lenalidomide plus dexamethasone compared with dexamethasone alone in patients with relapsed or refractory multiple myeloma. Presented at the 49th Annual Meeting and Exposition of the American Society of Hematology. December 8–11, 2007; Atlanta, GA.
22. Palumbo A, Miguel JS, Sonneveld P, et al. Lenalidomide: a new therapy for multiple myeloma. *Cancer Treat Rev.* 2008 Jan 28 [Epub ahead of print].
23. Mark T, Jayablan D, Pearse RN, et al. Cyclophosphamide overcomes the suppressive effect of lenalidomide therapy on stem cell collection in preparation for autologous stem cell transplantation for multiple myeloma. Presented at the 49th Annual Meeting and Exposition of the American Society of Hematology. December 8–11, 2007; Atlanta, GA.
24. 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;21:2035-2042.
25. Attal M, Harousseau JL, Facon T, et al; InterGroupe Francophone du Myélome. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2003;349:2495-2502.
26. Barlogie B, Tricot GJ, van Rhee F, et al. Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. Br J Haematol. 2006;135:158-164.
27. Bahlis NJ, Song K, Trieu Y, et al. Lenalidomide overcomes poor prognosis conferred by del(13q) and t(4;14) in multiple myeloma: results of the Canadian MM016 trial. Presented at the 49th Annual Meeting and Exposition of the American Society of Hematology. December 8–11, 2007; Atlanta, GA.
28. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood*. 2007;109:3489-3495.
29. Harousseau JL, Weber DM, Dimopoulos M, et al. Relapsed/refractory multiple myeloma patients treated with lenalidomide/dexamethasone who achieve a complete or very good partial response have longer time to progression compared with patients achieving a partial response. Presented at the 49th Annual Meeting and Exposition of the American Society of Hematology. December 8–11, 2007; Atlanta, GA.
30. Alexanian R, Weber D, Giralt S, et al. Impact of complete remission with intensive therapy in patients with responsive multiple myeloma. *Bone Marrow Transplant*. 2001;27:1037-1043.
31. O'Shea D, Giles C, Terpos E, et al. Predictive factors for survival in myeloma patients who undergo autologous stem cell transplantation: a single-centre experience in 211 patients. *Bone Marrow Transplant.* 2006;37:731-737.

Commentary:

Lenalidomide and Dexamethasone for the Treatment of Multiple Myeloma

Thierry Facon, MD

Professor
Lille University Hospital
Lille, France

Multiple myeloma remains incurable despite conventional chemotherapy. Lenalidomide is a functional derivative of thalidomide that is more potent than thalidomide in cytokine modulation, T-cell proliferation, host immunoregulatory augmentation, and antiangiogenic properties.[1] In addition, lenalidomide is more potent than thalidomide in inhibiting myeloma cell proliferation in vitro.[2] Based on laboratory results, two phase I clinical trials with lenalidomide were initiated in 2001, one at the University of Arkansas and the second at the Dana-Farber Cancer Center. These studies showed that the maximum tolerated dose was 25 mg daily. In the Arkansas study, 8 of 15 patients with relapsed or refractory multiple myeloma (53%) responded to treatment.[3] In the Dana-Farber study, 17 of 24 patients (71%) responded to treatment.[4] These results were considered promising because most patients had failed other regimens, including thalidomide. A multicenter randomized phase II trial of lenalidomide in patients with relapsed or refractory multiple myeloma was then conducted comparing two doses of lenalidomide: 30 mg once a day versus 15 mg twice daily (for 3 weeks followed by one week rest).[5] The ORR to lenalidomide alone was 25% (24% for once-daily and 29% for twice-daily lenalidomide). Among the nonresponders, an additional 29% responded once dexamethasone was added to the regimen. Increased severe myelosuppression was noted in patients receiving 15 mg twice daily. Median PFS and OS were 7.7 and 28 months, respectively, on the 30 mg once-daily arm. Significant neuropathy and DVT each occurred in only 3% of patients. This study formed the basis for future studies with lenalidomide, alone or in combination with dexamethasone.

The most important studies at the present time are the two phase III studies of lenalidomide and dexamethasone versus dexamethasone alone in patients with relapsed or refractory multiple myeloma: MM-009 in North America[6] (principal investigator D. Weber, The University of Texas M. D. Anderson Cancer Center) and MM-010 in Europe, Australia, and Israel[7] (principal investigator M. Dimopoulos, Athens, Greece). This international effort resulted in approval for lenalidomide in the US and Europe for first-relapse use, as well as in the recent back-to-back publication in the *New England Journal of Medicine*. Both studies showed the superior efficacy of lenalidomide plus dexamethasone versus high-dose dexamethasone in terms of response rate, including CR rate, TTP, and OS. MM-009 and MM-010 had a very rigorous assessment of efficacy and safety and, importantly, their results were very concordant.

Pooled analyses of MM-009 and MM-010 are now available as well as analyses of specific patient populations such as patients in first relapse, with renal failure, or with prior exposure to thalidomide.[8] The pooled 61% response rate in the lenalidomide group and the median TTP of 11.2 months are among the highest values that have been reported in the treatment of relapsed/refractory multiple myeloma. Patients from both studies were also pooled for an updated survival analysis. Despite 47% of patients crossing over to the lenalidomide-dexamethasone arm at progression or at the time of unblinding, OS was significantly improved in patients treated with lenalidomide plus dexamethasone compared to dexamethasone alone. Median survival in the lenalidomide group was 35 months versus 31 months in the dexamethasone-alone group. This 35-month median survival is among the longest survivals ever reported for relapsed/refractory multiple myeloma patients. As a comparison, in a recent report from the Mayo Clinic, patients relapsing after high-dose therapy before December 2000 had a median survival of 1 year.[9]

The benefits of the lenalidomide-dexamethasone combination were most marked in patients in first relapse. In this group the ORR was 65%, with approximately 30% CR or nCR, the median TTP was 14.5 months, and an unprecedented 39.1-month median survival time was achieved. Results were also encouraging for patients with prior exposure to thalidomide, including those resistant to this agent. The 50% response rate achieved in this latter group, despite the fact that the patients had more advanced disease, was in line with the higher preclinical potency demonstrated by lenalidomide as compared to thalidomide. Lenalidomide was also equally effective in patients with or without prior ASCT and regardless of age and renal function. The primary toxic effects of lenalidomide were hematologic and manageable with dose adjustment of the drug. Myelosuppression was more marked after transplantation

and in patients with severe renal impairment. Of note, in the pooled analysis, the rate of thromboembolic events was unrelated to the concomitant use of erythropoietin; the prophylactic effect of aspirin is still unclear. Adverse events were equally frequent across age groups.

Another interesting post hoc analysis considered the subgroup of patients achieving a CR or VGPR compared to those having only a PR.[10] Until now, the strong relationship between quality of response and OS had mostly been shown in newly diagnosed patients treated with high-dose chemotherapy. In fact, up to now the number of patients with relapsed/refractory multiple myeloma who achieved at least a VGPR was too small to show any differences—but this scenario is rapidly changing with the use of novel agents. In the MM-009/MM-010 pooled analysis, the 114 patients treated with lenalidomide plus dexamethasone who achieved a CR or VGPR had improved duration of response and TTP compared to the 100 patients who achieved only a PR. In addition, a trend toward improved survival was noted. The study also analyzed the distribution over time of response achievement and suggested that maintaining patients on lenalidomide plus dexamethasone resulted in the occurrence of late high-quality responses beyond the first year of treatment. This issue clearly warrants further investigation. If correct, it would indicate for the lenalidomide/dexamethasone regimen the ability to obtain both rapid responses—useful for patients with rapidly progressing disease—and long-term disease control through sustained and as well as late CRs/VGPRs.

Over the past few years, cytogenetic abnormalities, especially the t(4;14) translocation and the 17p deletion, have been recognized as adversely impacting the survival of newly diagnosed multiple myeloma patients.[11] The ability of novel agents to overcome the poor prognosis conferred by these chromosomal aberrations is a major issue for the future. The Canadian MM-016 retrospective study was designed to look at the effect of lenalidomide in relapsed/refractory patients with or without these cytogenetic abnormalities.[12] Overall, high-risk patients, defined as those with t(4;14) and/or del(17q), did not have a worse prognosis when treated with lenalidomide plus dexamethasone. This study should be regarded as suggestive, as the number of patients was relatively small; other studies are warranted to confirm this preliminary result.

Following the promising results obtained in relapsed/refractory multiple myeloma, lenalidomide was rapidly moved up to the first-line, in combination with melphalan-prednisone or dexamethasone.[13,14] The phase II study of lenalidomide and dexamethasone for newly diagnosed patients was initiated in 2004 and the 3-year survival in the first series of 34 patients remains as high as 88%.[15] The ECOG E4A03 study comparing lenalidomide and high-dose dexamethasone versus lenalidomide and low-dose dexamethasone was also very important, especially for the improvement of dexamethasone management. It unequivocally established that the lower dose of dexamethasone is safer and results in a better overall survival. As a consequence, the study is also considered important for the fate of all dexamethasone combinations. The study was not designed to test efficacy of long-term lenalidomide/dexamethasone treatment, especially because some patients received ASCT after induction with lenalidomide/dexamethasone, but the 2-year survival rate in the low-dose dexamethasone arm was 87%, the highest so far reported. Overall, ease of delivery, high response and survival rates, and manageable adverse events make lenalidomide plus dexamethasone an excellent front-line therapeutic choice. Very recently, efforts have been made to further improve the combination. Cyclophosphamide plus G-CSF has been suggested as the optimal stem cell mobilization regimen after lenalidomide induction.[16]

Many other combination therapies continue to be explored and promise further improvements.[17] The results of several trials considering lenalidomide consolidation or maintenance therapy are eagerly anticipated. For example, the MM-020/IFM 07/01 trial will compare lenalidomide plus low-dose dexamethasone for 18 cycles versus the same combination on a continuous basis versus the combination of melphalan, prednisone, and thalidomide. The results of this three-arm study will yield important data as we continue to hone the optimal treatment regimens for patients with multiple myeloma.

References

1. Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nat Rev Cancer*. 2004;4:314-322.
2. Hideshima T, Chauhan D, Shima Y, et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood*. 2000;96:2943-2950.
3. Zangari M, Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. *Blood*. 2001;98:1614-1615.
4. 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;100:3063-3067.
5. 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;108:3458-3464.
6. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357:2133-2142.
7. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357:2123-2132.
8. Weber DM, Knight R, Chen C, et al. Prolonged overall survival with lenalidomide plus dexamethasone compared with dexamethasone alone in patients with relapsed or refractory multiple myeloma. *Blood*. 2007;110:128a. Abstract 412.
9. Kumar S, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, et al. Improving survival in multiple myeloma: impact of novel therapies. *Blood*. 2007;110:1051a.
10. Harousseau JL, Weber DM, Dimopoulos M, et al. Relapsed/refractory multiple myeloma patients treated with lenalidomide/dexamethasone who achieve a com-

plete or near complete response have longer overall survival and time to progression compared with patients achieving a partial response. *Blood*. 2007;110:1052a. Abstract 3598.
11. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. *Blood*. 2007;109:3489-3495.
12. Bahlis NJ, Song K, Trieu Y, et al. Lenalidomide overcomes poor prognosis conferred by del13q and t(4;14) but not del17p13 in multiple myeloma: results of the Canadian MM016 trial. *Blood*. 2007;110:1052a. Abstract 3597.
13. 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;25:4459-4465.
14. Rajkumar S, Jacobus S, Callander N, et al. A randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinates by the Eastern Cooperative Oncology Group. *Blood*. 2007;110:31a. Abstract 74.
15. 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;82:1179-1184.
16. Mark T, Jayabalan D, Pearse R, et al. Cyclophosphamide overcomes the suppressive effect of lenalidomide therapy on stem cell transplantation for multiple myeloma. *Blood*. 2007;110:888a. Abstract 3024.
17. Kumar S, Hayman SR, Buadi F, et al. Phase II trial of lenalidomide, cyclophosphamide, and dexamethasone for newly diagnosed myeloma. *Blood*. 2007;110:64a. Abstract 190.


H&O