

activating factor (BAFF) is a key player in this loop. BAFF is a tumor necrosis factor (TNF)-related ligand secreted by OCs and BMSCs that supports MM cell growth and stromal cell adhesion. In vivo, an anti-BAFF neutralizing antibody inhibited MM cell growth, leading to prolonged survival. Importantly, it reduced the number of OCs as well as osteolytic lesions in a mouse model of humanized MM bone disease.<sup>4</sup> Therefore, BAFF is a promising target in MM bone disease; clinical trials are ongoing to evaluate the effects of neutralizing BAFF antibody in patients with MM. Finally, the immunomodulatory compound lenalidomide has been studied for its anti-OC effect mediated by inhibition of PU.1, a critical transcription factor in OC differentiation.<sup>5</sup> Until recently, the focus of research has been on the OC axis, with the OB axis remaining largely underexploited. Recent studies have demonstrated that stimulation of OB differentiation results in a hostile environment for MM cells, which leads to reduced plasma cell growth. Indeed, in vitro and in vivo assays showed that OBs do not support MM cell proliferation when compared with either OCs or BMSCs. The proteasome inhibitor bortezomib is a widely used anti-MM drug. It inhibits MM cells directly as well as indirectly by modifying their microenvironment. By inhibition of protein degradation and consequent restoration of  $\beta$ -catenin levels, low doses of bortezomib potently stimulate OB differentiation from BMSCs and overcome the inhibitory effect of MM cells on OBs.<sup>6,7</sup> Importantly, alkaline phosphatase levels, a parameter of OB differentiation, correlated with response to bortezomib, suggesting that modifications of the bone microenvironment could lead to a reduction in tumor burden. A critical player in MM-mediated bone disease is dickopf-1 (DKK1), an inhibitor of WNT signaling pathway that prevents OB differentiation. High levels of DKK1 are observed in bone marrow plasma of MM patients with active bone disease compared with monoclonal gammopathy of unknown significance and normal donors. DKK1 is secreted mainly by primary MM cells and it promotes interleukin-6 secretion by inhibiting BMSC differentiation in OBs. Neutralizing antibody anti-DKK1 stimulates OB differentiation both in vitro and in vivo in the presence of MM,<sup>8,9</sup> rescuing bone disease in an in vivo model of MM. DKK1 inhibitors are currently undergoing phase I clinical trials in MM patients with bone disease. We have recently identified activin A as another promising target in MM bone disease. Activin A is a transforming growth factor-B superfamily member involved in bone catabolism, with both pro-OC and anti-OB effects. Its levels are increased in bone marrow plasma of MM patients with osteolytic lesions; in contrast to DKK1, activin A is synthesized and secreted mainly by BMSC and OC cells. Importantly, adhesion of MM cells to BMSCs further enhanced its secretion. Inhibition of activin A by a soluble receptor promotes OB differentiation and overcomes myeloma-induced OB inhibition. In vivo, it translates in improved bone density and decreased osteolytic lesions in a mouse model of humanized MM bone disease. Importantly, activin A inhibition reduces MM growth in the context of the microenvironment both in vitro and in vivo.<sup>10</sup> Because an unbalanced OC/OB axis characterizes MM, new treatment strategies should focus on promoting OB differentiation while inhibiting OC activity. Agents such as activin A inhibitors with dual effects on OC and OB differentiation are particularly promising for restoring bone homeostasis in MM. Other approaches rely on the combination of anabolic and anticatabolic agents. Indeed, ongoing trials are combining

anti-BAFF neutralizing antibodies with bortezomib, with the purpose of restoring physiologic bone remodeling in patients with MM. These combined approaches along with optimal use of BP will result not only in alleviating SRE, but more importantly, may also contribute to improved antitumor activity in future clinical trials.

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### Pomalidomide (CC4047) plus Low-Dose Dexamethasone (Pom/Dex) as Therapy for Relapsed Multiple Myeloma

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### Introduction

The introduction of thalidomide represented a major milestone in the treatment of multiple myeloma. Thalidomide was initially used for treatment of multiple myeloma because of its antiangiogenic properties.<sup>1</sup> Promising clinical results led to the development of a class of thalidomide analogues termed immunomodulatory drugs. In relapsed myeloma, single thalidomide has response rates of 30%-35%.<sup>1,2</sup> The addition of dexamethasone to thalidomide improves responses to 40%-50%.<sup>3</sup> Lenalidomide and pulse dexamethasone have response rates of 55%-60%,<sup>4,5</sup> in relapsed myeloma and rates of 90% in newly diagnosed myeloma.<sup>6,7</sup> CC4047 (pomalidomide) is the newest

immunomodulatory drug. Phase I trials established that the agent is well tolerated in doses ranging from 1-5 mg per day.<sup>8</sup> We report on the first phase II trial of pomalidomide combined with low-dose dexamethasone in patients with relapsed or refractory multiple myeloma.

## Methods

Thirty-seven patients (21 male and 16 female) were enrolled. Pomalidomide was given orally 2 mg daily on days 1-28 of a 28-day cycle. Dexamethasone was given orally at a dose of 40 mg daily on days 1, 8, 15, and 22 of each cycle. The primary endpoint of this trial is the proportion of confirmed responses. A confirmed response is defined to be a complete response (CR), partial response (PR), or very good partial response (VGPR) rate, as assessed by the International Myeloma Working Group Uniform Response criteria. The regimen would be declared effective if at least 11 responses were observed out of 37 patients using a single-stage phase II design. All patients received aspirin 325 mg daily as prophylaxis against deep-vein thrombosis. After the first 37 patients were enrolled a second cohort of 23 patients were added to gain additional information about toxicity and to gain insight as to whether increasing the dose from 2 mg per day to 4 mg per day in nonresponders is effective.

## Patient Population

Among all 60 patients enrolled, the median age was 66 years (range, 35-88 years). All patients were evaluable for response and toxicity, and all analysis was done on an intent-to-treat basis. All patients had received previous therapy: 35% had 3 previous regimens; 37% had 2 previous regimens, and 28% had 1 previous regimen. Sixty-five percent of patients had previous autologous stem cell transplantation (ASCT), including 30 patients who had 1 previous ASCT and 9 who had 2 previous ASCTs. Thirty-six patients (60%) had previous immunomodulatory drug therapy. The median time from diagnosis to enrollment in the study was 44 months.

## Toxicity

Toxic effects were graded according to the National Cancer Institute's Common Toxicity Criteria, version 3. Toxicity consisted primarily of myelosuppression. Grade 3 or 4 hematologic toxicity included neutropenia in 18 patients (30%), anemia in 2 patients (3%), and thrombocytopenia in 1 patient (1.6%). The most common grade 3/4 nonhematologic toxicity consisted of fatigue (12%) and pneumonia (7%). Other grade 3/4 nonhematologic toxicities seen in less than 5% of patients included diarrhea, atrial fibrillation, dehydration and renal insufficiency, constipation, hyperglycemia, and dizziness. Twenty-five percent of patients had neuropathy, including 12 patients with grade 1 (20%) neuropathy and 3 (5%) with grade 2 neuropathy. There was grade 3 or 4 neuropathy. No patients have had thromboembolic events. Two patients died on study. One patient, an 88-year-old female, died 3.3 months after initiating study treatment. This patient began study treatment 86 months after diagnosis and had received one previous chemotherapy regimen. Lytic lesions, high bone marrow labeling index, and high  $\beta_2$  microglobulin were observed at baseline. This patient maintained stable disease for 2 cycles before passing away as a result of valvular heart disease not related to study treatment. The second patient, an 82-year-old female, developed neutropenic fever

and pneumonia requiring mechanical ventilation during cycle 1. Her death from infection was attributed to her treatment.

## Efficacy

Among the first 37 patients enrolled, objective responses were seen in 23 patients (62%), including 9 (24%) with VGPR; 14 patients (38%) with PR; and 6 (16%) with stable disease. Objective responses were seen in 4 of 13 patients (29%) who were refractory to lenalidomide. Based on this, the trial was expanded to include 23 additional patients, for a total of 60 patients. With a median follow-up of 3.6 months (range, 0-9.6 months), objective responses were seen in 35 patients (58%), including PR in 20 patients (33%), VGPR in 14 patients (23%), and CR in 1 patient (2%). Eleven patients are stable, and 1 patient is inevaluable for response. Forty-three patients continue to receive treatment. Thirteen have progressed.

## Discussion

The combination of pomalidomide and low-dose dexamethasone is highly active and well tolerated in the treatment of relapsed/refractory multiple myeloma. Lenalidomide was approved by the Food and Drug Administration and the European Medicines Agency based on the results of 2 randomized phase 3 trials that showed that the combination lenalidomide and dexamethasone (len/dex) was superior to dexamethasone alone.<sup>4,5</sup> Much of the toxicity of the len/dex regimen was due to the high-dose pulse dexamethasone. The Eastern Cooperative Oncology Group has recently reported results of a randomized phase 3 trial that shows that lenalidomide with weekly dexamethasone is safer and is associated with improved survival in patients with newly diagnosed multiple myeloma.<sup>9</sup> The choice to use low-dose weekly dexamethasone in our trial was based on these results. Here we report objective response rates that are similar to what has been seen in the trials of lenalidomide with high-dose pulse dexamethasone. Toxicity in our trial has been mild and consists primarily of myelosuppression with neutropenia. Importantly, we are seeing responses in patients who have been shown to be lenalidomide refractory. Based on this, we plan to open a phase II trial of pomalidomide and dexamethasone for lenalidomide-refractory patients.

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