Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease

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Pomalidomide at doses of 2 or 4 mg/d has demonstrated excellent activity in patients with multiple myeloma (MM). We opened 2 sequential phase 2 trials using the pomalidomide with weekly dexamethasone (Pom/dex) regimen at differing doses to study the efficacy of this regimen in patients who have failed both lenalidomide and bortezomib. Pomalidomide was given orally 2 or 4 mg daily with dexamethasone 40 mg weekly. Thirty-five patients were enrolled in each cohort. Confirmed responses in the 2-mg cohort consisted of very good partial response (VGPR) in 5 (14%), partial response (PR) in 4 (11%), minor response (MR) in 8 (23%) for an overall response rate of 49%. In the 4-mg cohort, confirmed responses consisted of complete response (CR) in 1 (3%), VGPR in 3 (9%), PR in 6 (17%), MR in 5 (14%) for an overall response rate of 43%. Overall survival at 6 months is 78% and 67% in the 2- and 4-mg cohort, respectively. Myelosuppression was the most common toxicity. This nonrandomized data suggests no advantage for 4 mg over the 2 mg daily. Pomalidomide overcomes resistance in myeloma refractory to both lenalidomide and bortezomib. This trial is registered at http://ClinicalTrials.gov, number NCT00558896. (*Blood*. 2011;118(11): 2970-2975)

Introduction

The introduction of thalidomide was crucial in the treatment of myeloma.[1] Promising clinical results led to the development of a class of thalidomide analogues termed immunomodulatory drugs (IMiDs), including lenalidomide and pomalidomide. The availability of novel therapeutic agents has favorably affected the survival of patients with myeloma.[2] Pomalidomide is the newest IMiD, and has single-agent activity in relapsed myeloma.[3,4]

Our earlier studies demonstrated that pomalidomide, 2 mg daily, with weekly dexamethasone (Pom/dex) has excellent activity in relapsed myeloma.[5] Subsequent trials confirmed activity in patients with relapsed disease who were refractory to lenalidomide.[6] Follow-up trials have focused on determining the optimal dosing schedule of this agent to maximize clinical benefit. This led to trials with pomalidomide at doses of 4 mg, either continuously or for 21 of 28 days[7,8] as salvage therapy for patients with heavily pretreated relapsed myeloma.

The goals of this nonrandomized study were to determine whether the Pom/dex regimen was effective in patients refractory to both bortezomib and lenalidomide (dual-refractory myeloma) and to ascertain whether starting with a higher dose (4 mg daily) yields better response rates compared with the lower starting dose (2 mg daily) that we have used in earlier trials. We report on 2 sequential phase 2 trials of Pom/dex that addressed these questions.

Methods

Eligibility

Patients were eligible to enter on the study if they had previously treated, symptomatic multiple myeloma (MM). Patients had to be refractory to lenalidomide and bortezomib therapy. For this purpose, refractory disease was defined as relapse on or within 60 days of stopping treatment. Patients were required to have measurable disease defined by one of the following: serum monoclonal protein > 10 g/L, serum immunoglobulin free light chain (FLC) > 10 mg/dL and an abnormal FLC ratio, urine light chain excretion ≥ 200 mg/24 hours, measurable soft-tissue plasmacytoma that had not been radiated, or $> 30\%$ plasma cells in BM. Patients also needed platelet count $> 75 \times 10^9$/L, absolute neutrophil count $> 1.0 \times 10^9$/L, and creatinine $< 221\mu$M (2.5 mg/dL). All previous cancer therapy, including chemotherapy and an investigational agent, must have been discontinued ≥ 2 weeks before study registration. Patients with uncontrolled infection, another active malignancy, deep vein thrombosis that had not been therapeutically anticoagulated, Eastern Cooperative Oncology Group (ECOG) performance score of 3 or 4, grade 3 or 4 peripheral neuropathy, pregnant or nursing women, women of childbearing potential who were unwilling to use a dual method of contraception, and men who were unwilling to use a condom were excluded. The study was approved by the Mayo Clinic Institutional Review Board in accordance with federal regulations and the Declaration of Helsinki.

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Treatment schedule

Pomalidomide was given orally at a dose of 2 or 4 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. Patients also received aspirin 325 mg once daily for thromboprophylaxis. Patients were allowed to substitute full-dose anticoagulation with either low-molecular-weight heparin or warfarin at physician discretion. G-CSF was not allowed to avoid dose reductions but could be used if a patient developed neutropenic fever.

Dose adjustments were permitted based on toxicity as described. Pomalidomide was to be permanently discontinued in the event of a grade 4 rash, neuropathy, or hypersensitivity, and grade 3 or higher bradycardia or cardiac arrhythmia. Pomalidomide was progressively reduced for other related grade 3 or higher adverse events to dose levels of 2 or 4 mg for 21 days each 28-day cycle. Subsequently, doses were decreased by 1 mg for the 4-mg cohort until a dose of 2 mg for 21 days of each 28-day cycle was reached. Subsequent doses were decreased by 0.5 mg. When grade 3 or 4 adverse events occurred before day 15 of a cycle and resolved to grade 2 or lower before day 28 of the cycle, pomalidomide was resumed at the next lower dose level, with the next cycle continuing at the reduced dose level. For grade 3 or 4 adverse events occurring on or after day 15 of a given cycle, pomalidomide was held for the remainder of the cycle and reduced by one dose level beginning with the next cycle. Dose reductions were permitted for dexamethasone related toxicity, by lowering the dose of dexamethasone progressively to 20 mg, 12 mg, 8 mg, and 4 mg once weekly. Patients unable to tolerate the lowest doses of pomalidomide or dexamethasone needed to stop therapy with that agent permanently. In the absence of grade 3 or higher toxicity, the daily dose of pomalidomide could be increased at physician discretion to 4 mg in patients who had not achieved a 25% reduction in serum or urine monoclonal protein levels after 2 cycles of therapy or who had previously responded and had rising serum or urine monoclonal protein levels. Among patients who had a previous dose reduction, escalation was allowed as long as there was no current grade 3 or 4 toxicity.

Response and toxicity criteria

Responses were assessed according to published criteria of the International Myeloma Working Group.[9] A partial response (PR) was defined as $\geq$ 50% reduction in the level of the serum monoclonal (M) protein and/or a reduction in 24-hour urinary light chain excretion $\geq$ 90% or to $<$ 200 mg or as $\geq$ 50% reduction in BM plasma cells, if BM was the only measurable parameter at baseline, and baseline percentage was $\geq$ 30%. In addition to the these criteria, if a plasmacytoma was present at baseline, $\geq$ 50% reduction in the size of soft-tissue plasmacytomas was also required. Minor response (MR) was defined as $\geq$ 25% but $<$ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50%-89%, which still exceeds 200 mg per 24 hours In addition, if a plasmacytoma was present at baseline 25%-49% reduction in the size of soft tissue plasmacytomas was also required.

Complete response (CR) required complete disappearance of the monoclonal protein in the serum and urine by immunofixation studies and $<$ 5% plasma cells on BM examination. Stringent complete response (sCR) required CR plus normal FLC ratio and absence of clonal cells in BM by immunohistochemistry or immunofluorescence. A very good partial response (VGPR) required, in addition to criteria for PR, serum and urine M protein detectable only on immunofixation but not on electrophoresis or $\geq$ 90% reduction in serum M protein and 24-hour urine M protein $<$ 100 mg/24 hours. In patients in whom the only measurable disease was by serum FLC levels, CR required a normal FLC ratio of 0.26-1.65 in addition to CR criteria. VGPR in such patients was defined as a $>$ 90% decrease in the difference between involved and uninvolved FLC levels. All response categories (CR, sCR, VGPR, and PR) require 2 consecutive assessments made at any time before the institution of any new therapy.

Disease progression required any one of the following criteria: (1) increase in serum monoclonal protein by 25% or higher above the lowest response level and an absolute increase of $>$ 5 g/L, (2) increase in urine monoclonal protein by 25% above the lowest remission value and an absolute increase in excretion by 200 mg/24 hours or greater, (3) increase in size of soft-tissue plasmacytoma by $>$ 50% or appearance of a new plasmacytoma, (4) definite appearance of new bone lesions or increase in the size of existing bone lesions by $>$ 50%, or (5) unexplained hypercalcemia $>$ 2.875mM ($>$ 11.5 g/dL).

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 3, was used to grade adverse events as well as to assign perceived attribution to the study treatment regimen.

We were interested in specifically looking at responses among high-risk patients. High risk was defined, according published criteria[9] as cytogenetic studies (hypodiploidy or karyotypic deletion of chromosome 13), FISH (presence of translocations t(4;14) or t(14;16) or deletion 17p), or plasma cell labeling index (PCLI) $\geq$ 3%.

Statistical design and analysis

The primary end point for both cohorts was the proportion of confirmed responses (CR, VGPR, or PR). Both cohorts used a one-stage design with an interim analysis based on a Simon design. The 2-mg cohort tested that the true confirmed response rate was at most 45% versus the alternative that it was at least 65%, with a type 1 error of 10% and power of 85%. This cohort would be declared ineffective if a maximum of 18 confirmed responders were observed in the first 33 evaluable patients. An interim analysis was performed after the first 19 patients; if at most 8 confirmed responders were observed, the cohort would be considered ineffective. (accrual did not halt while waiting for interim analysis.) The 4-mg cohort tested that the true confirmed response rate was at most 25% versus the alternative that it was at least 45%, with a type 1 error of 10% and power of 88%. This cohort would be declared ineffective if a maximum of 11 confirmed responders were observed in the first 33 evaluable patients. An interim analysis was performed after the first 17 patients; if at most 3 confirmed responders were observed, the cohort would be considered ineffective (accrual did not halt while waiting for interim analysis). Secondary end points included overall survival (OS), progression-free survival (PFS), duration of response (DOR), and adverse event (AE) profile.

All analyses are based on an intent-to-treat principle. Exact binomial confidence intervals are constructed for the primary end point of confirmed response. The distributions of (1) OS time (time from study entry to death), (2) PFS time (time from study entry to earlier of disease progression or death), and (3) DOR (time from first documentation of response until disease progression or death), are estimated using the method of Kaplan-Meier. Simple descriptive statistics are used to summarize the AE profile and baseline characteristics.

Results

Patient population

Overall, 35 patients were accrued to the study from May 2009 to November 2009 and treated with a pomalidomide dose of 2 mg daily. An additional 35 patients were accrued from November 2009 to April 2010 and treated with a pomalidomide dose of 4 mg daily. All patients were evaluable. Patient characteristics and previous therapies at study entry are presented in Tables 1 and 2. The median number of prior regimens in each cohort was 6. All patients had previous bortezomib and lenalidomide therapy and were refractory to these agents. Baseline peripheral neuropathy was present in 29 (83%) and 24 (68%) 2 mg and 4 mg patients, respectively. The median time from diagnosis to enrollment on study was 57 months (2-mg cohort) and 72 months (4-mg cohort). Fifteen (56%) 2-mg patients and 21 (60%) 4-mg patients were classified as high risk using standard criteria (Table 1).[9]

Follow-up

The median number of cycles administered was 6 (range 1-17) for the 2-mg cohort and 3 (range 1-12) for the 4-mg cohort. Five patients in the 2-mg cohort and 4 patients in the 4-mg cohort continued to receive treatment. The major cause for stopping study

Table 1. Baseline characteristics

	2 mg (N = 35)	4 mg (N = 35)
Median age, y (range)	62.0 (39.0-77.0)	61.0 (45.0-77.0)
Sex		
Female	8 (22.9%)	14 (40%)
Male	27 (77.1%)	21 (60%)
ECOG performance score		
0	13 (37.1%)	13 (37.1%)
1	18 (51.4%)	18 (51.4%)
2	4 (11.4%)	4 (11.4%)
Median time from diagnosis to on study, mo (range)	57.0 (11.7-248.5)	71.6 (13.3-206.3)
Cytogenetics result		
Normal	15 (44.1%)	12 (36.4%)
Abnormal	13 (38.2%)	17 (51.5%)
Not done	6 (17.6%)	4 (12.1%)
FISH		
Normal	0	1 (3.1%)
Abnormal	25 (73.5%)	26 (81.3%)
Not done	9 (26.5%)	5 (15.6%)
FISH results*		
13q−	3 (9%)	4 (13%)
Del 17, 17p−	5 (15%)	7 (23%)
t(11,14)	7 (21%)	6 (19%)
t(4;14)	3 (9%)	6 (19%)
t(14;16)	0 (0%)	2 (6%)
Other	20 (59%)	21 (68%)
High risk	15 (55.6%)	21 (60%)
ISS stage at diagnosis		
1	6 (17.1%)	10 (28.6%)
2	18 (51.4%)	17 (48.6%)
3	11 (31.4%)	8 (22.9%)
Neuropathy at baseline		
Grade 0	6 (17%)	11 (32%)
Grade 1	24 (69%)	19 (54%)
Grade 2	5 (14%)	5 (14%)
ANC, K/μL	2.2 (1.1-8.7)	2.5 (1.1-6.9)
PLT, K/μL	106.0 (77.0-279.0)	134.0 (70.0-9200.0)
HGB, g/dL	10.0 (8.2-14.4)	10.6 (7.6-14.2)
WBC, K/μL	3.8 (1.7-10.6)	3.9 (1.8-8.8)
Creatinine, mg/dL	1.0 (0.8-2.2)	1.0 (0.6-2.0)
β2 microglobulin, μg/mL	4.0 (1.9-9.6)	3.5 (2.2-13.4)
CRP, mg/dL	3.3 (0.2-335.3)	6.3 (0.6-53.1)
BM labeling, %	2.6 (0.0-10.2)	1.8 (0.0-12.0)

ECOG indicates Eastern Cooperative Oncology Group; ISS, international staging system; ANC, absolute neutrophil count; PLT, platelet; HGB, hemoglobulin; WBC, white blood count; and CRP, c-reactive protein.

*FISH probes and locus for interphase clg FISH: 3cen (D3Z1), 7cen (D7Z1), 9cen (D9Z1), 15cen (D15Z4), 11q13 (CCND1-XT), 14q32 (IGH-XT), 13q14 (RB1), 13q34 (LAMP1), 14q32 (5′IGH,3′IGH), 17p13.1 (p53), 17cen (D17Z1).

drug was disease progression (25-2-mg and 21-4-mg patients). Four (2-2 mg/2-4 mg) patients withdrew because of physician or patient discretion. Four (2-2 mg/2-4 mg) patients have died, all because of disease progression. Four (1-2 mg/3-4 mg) patients withdrew because of adverse events. The median follow-up on the alive patients is 9.7 months (range: 1-18) in the 2-mg cohort and 6.6 months (range: 1-11) in the 4-mg cohort (Table 3). In the 2-mg cohort, 11 (31%) patients had dose reductions while in the 4-mg cohort, 12 (35%) patients dose reductions because of toxicity, primarily neutropenia.

Efficacy

Seven of the first 19 evaluable patients on the 2-mg cohort achieved a confirmed response; thus the trial did not meet the interim analysis efficacy rule. Per study design, accrual did not halt while data for interim analysis matured. Nine (27%; 95% confidence interval [CI]: 13-45) of the first 33 evaluable patients on the 4-mg cohort achieved a confirmed response (≥ PR), which did not meet the efficacy rule for study design. Confirmed responses (≥ MR) in the 2-mg cohort consisted of VGPR in 5 (14%), PR in 4 (11%), MR in 8 (23%) for an overall response rate of 49%. In the 4-mg cohort, confirmed responses (≥ MR) consisted of CR in 1 (3%), VGPR in 3 (9%), PR in 6 (17%), MR in 5 (14%) for an overall response rate of 43%. Stable disease was the best response in 12 (2-mg cohort) and 11 (4-mg cohort) patients. The median time to response was 1 month (range: 0.8-4) for the 2-mg cohort and 2 months (range: 0.9-7.2) for the 4-mg cohort. Sixteen patients in the 2-mg cohort increased the dose of pomalidomide from 2 mg/d to 4 mg/d. Among these 16, 2 patients improved from stable disease to MR after increasing pomalidomide. Between the 2 cohorts, 36 of 62 patients were considered high risk. Cytogenetics and FISH were not available in the other 8 patients. Responses were seen in 13 of these 36 (21%) and consisted of VGPR (5), PR (4), and MR (4).

The median duration of response for the 9 responding patients (≥ PR) in the 2-mg cohort has not been reached (median follow-up: 14 months, range: 8-18); duration of response is 3.9 months

Table 2. Previous therapies

	2 mg (N = 35)	4 mg (N = 35)
No. of prior chemotherapies		
2	0 (0%)	2 (5.7%)
3	3 (8.6%)	6 (17.1%)
4	4 (11.4%)	2 (5.7%)
5	10 (28.6%)	4 (11.4%)
6	4 (11.4%)	7 (20%)
7	10 (28.6%)	6 (17.1%)
8	3 (8.6%)	4 (11.4%)
9	1 (2.9%)	3 (8.6%)
11	0 (0%)	1 (2.9%)
Type of prior regimens		
Lenalidomide	35 (100%)	35 (100%)
Bortezomib	35 (100%)	35 (100%)
Thalidomide	22 (63%)	20 (57%)
Transplantation	27 (77%)	28 (80%)
Autologous	25	28
Allogeneic	2	0

Table 3. Follow-up

	2 mg (N = 35)	4 mg (N = 35)
Progression status		
No progression	9 (25.7%)	10 (28.6%)
Progression	26 (74.3%)	25 (71.4%)
Follow-up status		
Alive	25 (71.4%)	24 (68.6%)
Dead	10 (28.6%)	11 (31.4%)
Median follow-up, alive patients, mo (range)	9.7 (1.0-17.7)	6.6 (1.2-11.3)
Median no. of cycles administered per patient (range)	6.0 (1.0-17.0)	3.0 (1.0-12.0)
Currently receiving treatment	5 (14%)	4 (11%)
Reason for ending treatment		
Refused further treatment	1 (3.3%)	1 (3.2%)
Adverse event	1 (3.3%)	3 (9.7%)
Disease progression	25 (83.3%)	21 (67.7%)
Alternate treatment	0 (0%)	2 (6.5%)
Other medical problems	0 (0%)	2 (6.5%)
Died on study	2 (6.7%)	2 (6.5%)
Other	1 (3.3%)	0 (0%)

Table 4. Patient outcomes

	2 mg (n = 35)	4 mg (n = 35)
Confirmed response rate	26% (95% CI: 12-43)	28% (95% CI: 14-46)
No. of responders	9	10
CR	0	1
VGPR	5	3
PR	4	6
MR	8	5
SD	12	11
PD	3	8
NE	3	1
Median time to response	1 mo (range: 0.8-3.9)	1.7 mo (range: 0.9-7.2)
Overall survival*	NA	NA
Event free at 6 mo, %	78% (95% CI: 65-94)	67% (95% CI: 52-86)
Progression-free survival*	6.5 mo (95% CI: 3.9-8.9)	3.2 mo (95% CI: 1.9-8.6)
Event free at 6 mo, %	56% (95% CI: 41-75)	34% (95% CI: 21-55)

CI indicates confidence interval; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease; NE, not evaluable; and NA, not attained.

*Kaplan-Meier.

(95% CI: 1-NA; median follow-up: 6 months, range: 3-11) for the 10 responding patients in the 4-mg cohort. The median PFS was 6.5 months (95% CI: 3.9-8.9) in the 2-mg cohort and 3.2 months (95% CI: 1.9-8.6) in the 4-mg cohort. The median OS time has not yet been reached in either group. Overall survival at 6 months is 78% (95% CI: 65-94) in the 2-mg cohort and 67% (95% CI: 52-86) in the 4-mg cohort. Progression-free survival at 6 months is 56% (95% CI: 41-75; 2-mg cohort) and 34% (95% CI: 21-55; 4-mg cohort). Patient outcomes are summarized in Table 4.

Adverse events

Treatment was well tolerated. Toxicity consisted primarily of myelosuppression. Grade 3 or 4 hematologic toxicity regardless of attribution occurred in 83% (2-mg cohort) and 80% (4-mg cohort) and at least possibly attributed to the regimen occurred in 71% (2-mg cohort) and 74% (4-mg cohort). Grade 3 or 4 neutropenia (regardless of attribution) was seen in 51% (2-mg cohort) and 66% (4-mg cohort). Grade 3 or 4 nonhematologic toxicity regardless of attribution occurred in 69% (2-mg cohort) and 54% (4-mg cohort) and at least possibly attributed to the regimen was seen in 26% (2-mg cohort) and 26% (4-mg cohort). The most common nonhematologic toxicity was fatigue (2-mg cohort: 88%; 4-mg cohort: 91%) with grade 3/4 fatigue occurring in 9% of patients in both cohorts. Grade 3 pneumonia was reported in 11 (31%) patients in the 2-mg cohort; however, only 3 events were considered related to treatment. Pneumonia was reported in only 2 patients (grade 2 and 3) in the 4-mg cohort. Adverse events leading to study withdrawal consisted of rash (1 patient, 2-mg cohort), elevated bilirubin (1 patient, 4-mg cohort), neuropathy (1 patient, 4-mg cohort) and unspecified (1 patient, 4-mg cohort). Among the 2-mg cohort, 28 patients (80%) experienced neuropathy during treatment (18 grade 1; 10 grade 2). Six patients had worsening grade during treatment and 7 patients had neuropathy considered related to treatment. Among the 4-mg cohort, 31 (89%) patients experienced neuropathy during treatment (24 grade 1; 6 grade 2; 1 grade3). Ten had worsening grade during treatment and 11 patients had neuropathy considered related to treatment. Patients received aspirin 325 mg once daily for thromboprophylaxis. Patients were allowed to substitute full dose anticoagulation with either low molecular weight heparin or warfarin at physician discretion. Thromboprophylaxis consisted of aspirin in 68% of cycles among the 2-mg cohort and in 65% of cycles among the 4-mg cohort. For the majority of the remaining cycles, patients received full dose anticoagulation with either warfarin or heparin. Deep vein thrombosis occurred in 2 patients (6%; 2-mg cohort) and 1 patient (3%; 4-mg cohort). Adverse events are outlined in Table 5.

Discussion

We previously reported that pomalidomide and low-dose dexamethasone (Pom/dex) is highly active in relapsed MM, with an overall response rate (PR or better) of 63%.[5] Next, to establish lack of cross-resistance with lenalidomide, we treated a cohort of patients with lenalidomide refractory disease.[6] Among 34 patients enrolled, responses of $\geq$ PR were seen in 31% of patients. The median time to response was 2 months and response duration was 9.1 months. Despite these promising results, important questions remained on the activity of this combination in patients with dual-refractory myeloma (resistant to both bortezomib and lenalidomide) and whether the results can be further improved by increasing the starting dose to 4 mg. In this study, we have addressed these issues through 2 sequential phase 2 trials. Our results show that the pomalidomide plus low-dose dexamethasone combination is significantly active in dual-refractory myeloma at both dosing levels, but we did not observe any advantage with the higher dose.

Our results are important because patients with myeloma that is refractory to both bortezomib and thalidomide or lenalidomide have a poor prognosis with median survival of 9 months and event-free survival of 5 months.[10] Pomalidomide plus low-dose dexamethasone offers significant hope to these patients. Our results are supported by those from the MM-002 phase 1/2 study which included patients who had previously been treated with both bortezomib and lenalidomide and were refractory to their most recent regimen. Thirty-eight patients were enrolled in the phase 1 portion of the MM-002 trial, and a partial response or better was seen in 25%.[7] The phase 2 portion of MM-002 randomized patients to receive pomalidomide alone or with dexamethasone, and provided additional supporting evidence; a total of 221 patients were enrolled and data regarding efficacy have been reported for the first 120 patients. The pomalidomide regimen was: 4 mg/d on days1-21 of each 28-day cycle. Responses of PR or better were seen in 25%.[7] In this setting, pomalidomide, with or without dexamethasone, showed promising activity and manageable toxicity in patients who had received multiple previous rounds of therapy, including both bortezomib and lenalidomide.

Our study does not show an improvement in efficacy associated with a higher starting dose. However, we studied only the day 1-28 dosing schedule. Recently, the French Intergroup reported the

Table 5. Maximum severity of adverse events (regardless of attribution)

	2-mg cohort, %				4-mg cohort, %			
Body system/toxicity*	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 1**	**Group 2**	**Group 3**	**Group 4**
Hematology								
Anemia	26	49	26	0	37	37	23	3
Leukopenia	11	31	31	9	9	23	54	6
Lymphocyte count decreased	0	3	26	6	0	6	34	3
Neutrophil count decreased	11	23	40	11	6	20	34	31
Platelet count decreased	34	23	29	3	40	14	14	17
Infection/febrile neutropenia								
Febrile neutropenia	0	0	0	0	0	0	11	0
Pneumonia	0	0	31	0	0	3	3	0
Upper respiratory infection	0	0	6	0	0	0	0	0
Metabolic/laboratory								
Hyperglycemia	0	3	9	0	0	6	3	0
Hypercalcemia	0	0	3	3	0	0	0	3
Musculoskeletal								
Fracture	0	0	6	0	0	0	6	0
Neurology								
Agitation	0	6	3	0	0	0	0	0
Anxiety	0	6	0	0	0	3	0	0
Confusion	0	3	3	0	0	0	0	0
Dizziness	0	6	0	0	0	0	0	0
Depression	0	3	0	0	0	9	0	0
Insomnia	0	6	6	0	0	3	0	0
Peripheral sensory neuropathy	51	29	0	0	69	17	3	0
Tremor	0	6	0	0	0	0	3	0
Pain								
Back pain	0	0	3	0	0	0	9	0
Pulmonary								
Dyspnea	0	3	3	0	0	3	3	0
Renal/genitourinary								
Renal failure	0	0	11	0	0	0	0	0
Cardiovascular								
Atrial fibrillation	0	3	9	0	0	0	0	0
Thrombosis	0	3	3	0	0	0	3	0
Dermatology/skin								
Rash	0	6	0	0	0	0	0	0
Constitutional symptoms								
Fatigue	11	69	9	0	31	51	9	0
Sweating	0	0	0	0	0	6	0	0
Gastrointestinal								
Anorexia	26	3	0	0	26	9	0	0
Diarrhea	26	6	0	0	14	9	0	0
Dyspepsia	0	0	0	0	0	6	0	0
Nausea	23	9	0	0	11	6	0	0
Vomiting	20	0	0	0	9	3	0	0

*Common Terminology Criteria for Adverse Events Version 3.0.

IFM 2009-02 pomalidomide study which included myeloma patients who were symptomatic and progressing following at least 2 cycles of lenalidomide and 2 cycles of bortezomib (either separately or in combination) addressed the issue of dosing schedule.[8] Pomalidomide was given orally either at 4 mg/d on days 1-21 of each 28-day (arm A) or continuously on days 1-28 of each 28-day cycle (arm B). Dexamethasone was given orally at 40 mg daily on days 1, 8, 15, and 22 of each cycle. Ninety-two were enrolled. Among 84 evaluable patients, responses of PR or better were seen in 42% (arm A) and 39% (arm B). Although our trials were sequential, not randomized, results reported here cannot confirm an advantage in starting with a more intense dosing schedule of pomalidomide. Response rates are similar with slightly higher toxicity in the group that received pomalidomide 4 mg daily.

As new drugs and regimens become available for myeloma, it is critical to evaluate response rates and toxicity in the context of how heavily pretreated and refractory to treatment the patient population is. Not surprising is the observation that the best response rates are seen in the trials with the fewest number of prior regimens (Table 6). Myelosuppression in both cohorts reported here is more pronounced than what has been reported in previous pomalidomide trials. The rate of grade 3 or 4 neutropenia was 51% in the 2-mg cohort and 66% in the 4-mg cohort. This compares to 32% in a population with 1-3 prior regimens and 26% in a lenalidomide refractory group. The higher rate in the current trials is most likely because of the refractoriness of the patient population. The median number of prior regimens is 6 with 80% and 77% having 4 or more prior regimens in the 2-mg and 4-mg cohorts, respectively. The etiology of the myelosuppression is multifactorial, reflecting a combination of poor marrow reserve, the aggressiveness of the underlying myeloma, as well as the toxicity of the regimen. A significant number of patients developed pneumonia while on

Table 6. Response rates with Pom/Dex according to number of prior regimens

	Median no. of prior regimens	Regimen	N	Schema	Doses, mg	≥ PR, %
Lacy[5]	2	Pom/Dex	60	28/28	2	63
Leleu[8]	4	Pom/Dex	43	21/28	4	42
	4		41	28/28	4	39
Lacy[6]*	4	Pom/Dex	34	28/28	2	32
Richardson[7]	5	Pom +/−	120	21/28	4	25
Phase 2		Dex				
Richardson[7]	6	Pom +/−	38	21/28	4	25
Phase 1		Dex			MTD	
Current study†	6	Pom/Dex	35	28/28	2	26
	6		35		4	28

Pom/Dex indicates pomalidomide, 2 mg daily, with weekly dexamethasone; PR, partial response; and MTD, maximal tolerated dose.
*Lenalidomide refractory.
†Lenalidomide and bortezomib refractory.

study. However, only a minority of these episodes were attributed to study drug by the treating physicians. The difference in pneumonia rates between the cohorts was likely because of the longer follow-up in the 2-mg cohort. Similarly, the absolute number of dose reductions was similar between the groups but the follow-up in the 2-mg cohort was longer suggesting a higher rate of dose reductions in the 4-mg cohort. The rate of neuropathy and thromboembolic disease seen in these cohorts is similar to what has been previously reported for pomalidomide in myeloma.

While the study design goals were not met for either cohort, the data presented here again confirms remarkable activity of the Pom/dex regimen. The results of this study indicate that pomalidomide will be a significant drug, covering an unmet clinical need: salvage therapy for patients with disease refractory to both lenalidomide and bortezomib. Objective responses were seen in 43%-49% of a heavily pretreated refractory population and 31% of high-risk patients, a population particularly resistant to treatment at the time of relapse. Responses were durable. The overall survival rates of 78% and 67% at 6 months are far superior to what would be expected for myeloma at this advanced stage. Although it is not clear that a dose of 4 mg for 28 continuously has any advantages over the 2-mg dose, we are exploring further whether a regimen of 4 mg for 21 of 28 days is superior to 2 mg continuously. Longer follow-up and randomized trials will be needed to answer this question.

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Authorship

Contribution: M.Q.L., S.V.R., and J.R.M. designed the trial, collected and analyzed data, and wrote the manuscript; statisticians J.B.A., K.L., and S.J.M. collected and analyzed the data, and provided critical review and edits to the manuscript; and M.Q.L., M.A.G., S.R.H., K.D.S., F.B., A.D., S.K., P.R.G., J.A.L., S.J.R., D.D., S.Z., R.F., P.L.B., V.R., A.K.S., C.R., S.V.R., and J.R.M. provided study patients, and provided critical review and edits to the manuscript.

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