

CLINICAL TRIALS AND OBSERVATIONS

Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib

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Key Points

- Pomalidomide with/without dexamethasone has promising activity and manageable toxicity in relapsed and refractory multiple myeloma patients.

This phase 1 dose-escalation study determined the maximum tolerated dose (MTD) of oral pomalidomide (4 dose levels) administered on days 1 to 21 of each 28-day cycle in patients with relapsed and refractory multiple myeloma (RRMM). After four cycles, patients who progressed or had not achieved minimal response (serum and urine M-protein reduction of $\geq 25\%$ and $\geq 50\%$) could receive dexamethasone 40 mg per week. Safety and efficacy were evaluated. Thirty-eight patients who had received both bortezomib and lenalidomide (median 6 prior therapies) were enrolled; 63% were refractory to both lenalidomide and bortezomib. There were four dose-limiting toxicities (grade 4 neutropenia) at 5 mg per day and so the MTD was 4 mg per day. Rates of

peripheral neuropathy and venous thromboembolism were low ($\leq 5\%$). Among the 38 patients enrolled (including 22 with added dexamethasone), 42% achieved minimal response or better, 21% achieved partial response or better, and 3% achieved complete response. Median duration of response, progression-free survival, and overall survival were 4.6, 4.6, and 18.3 months, respectively. Pomalidomide 4 mg per day on days 1 to 21 of each 28-day cycle, with or without dexamethasone (40 mg/week), has encouraging activity with manageable toxicity in RRMM, including those refractory to both lenalidomide and bortezomib. This study is registered at <http://www.clinicaltrials.gov> as #NCT00833833. (*Blood*. 2013;121(11):1961-1967)

Introduction

The introduction of novel agents including thalidomide, bortezomib, and lenalidomide has significantly improved survival outcomes for patients with multiple myeloma (MM)¹; however, almost all patients with MM eventually relapse and survival times shorten progressively with each subsequent relapse.²⁻⁴ The prognosis for patients who are refractory to novel agents is especially poor: patients who are refractory to bortezomib, lenalidomide, and thalidomide have a median overall survival (OS) of 9 months and an event-free survival of 5 months.³ Therefore, effective new treatments that reestablish tumor response are urgently required to improve outcomes for these patients.^{4,5}

Pomalidomide is a new immunomodulatory agent with significant in vitro antiproliferative⁶⁻¹¹ and proapoptotic effects.^{8,12} Recent studies have indicated limited cross-resistance between lenalidomide and pomalidomide.¹³ Several phase 1 and phase 2 studies evaluating continuous (2 mg/day) or alternate (5 mg/day) dose schedules of pomalidomide in patients with both relapsed and refractory (RR) MM have been reported.^{5,14-17} Pomalidomide plus low-dose dexamethasone has shown activity in patients with advanced MM who have relapsed after multiple lines of therapy, including those who are refractory to both lenalidomide and bortezomib.^{5,16}

This open-label, phase 1, dose-escalation study was conducted to evaluate the maximum tolerated dose (MTD) of pomalidomide when given for 21 days of each 28-day cycle in patients with RRMM who had previously received multiple lines of treatment, including bortezomib and lenalidomide. The primary objective of the study was to determine the MTD, and the secondary objectives were to evaluate the safety and activity of pomalidomide, with or without dexamethasone, in this population.

Materials and methods

Patient population

Patients aged ≥ 18 years, with RRMM and an Eastern Cooperative Oncology Group performance status score of < 2 were eligible. All patients had to have received prior treatment that included ≥ 2 cycles of lenalidomide and ≥ 2 cycles of bortezomib (in separate regimens or within the same combination regimen). Patients must have received ≥ 2 prior therapies, and have relapsed after having achieved at least stable disease (SD) for a minimum of one treatment cycle of a prior regimen before developing progressive disease

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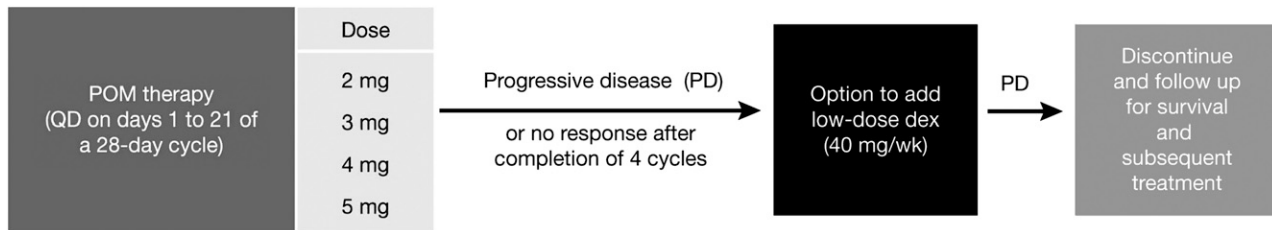


Figure 1. The design of the phase 1 dose-escalation study in patients with RRMM. dex, dexamethasone; POM, pomalidomide; QD, one a day; wk, week.

(PD). Patients must have progressed on or within 60 days of the last treatment regimen used before enrollment (to define occurrence of refractory disease). Eligible patients had measurable levels of M-protein in the serum (≥ 0.5 g/dL) or urine (≥ 0.2 g/day) at study entry.

Patients were excluded if they had an absolute neutrophil count (ANC) of $< 1000/\mu\text{L}$; platelet counts of $< 75\,000/\mu\text{L}$ (in patients in whom $< 50\%$ of bone marrow nucleated cells were plasma cells) or $< 30\,000/\mu\text{L}$ (in patients in whom $\geq 50\%$ of bone marrow nucleated cells were plasma cells); a serum creatinine level of ≥ 3.0 mg/dL; serum transaminase levels > 3 times the upper limit of normal (ULN); and a serum total bilirubin level of > 2.0 mg/dL. Patients were also excluded if they had grade ≥ 2 peripheral neuropathy (PN) or known hypersensitivity to lenalidomide, thalidomide, or dexamethasone.

The study was approved by the institutional review boards of the participating centers, overseen by a data safety monitoring committee, and conducted according to the Declaration of Helsinki International Conference on Harmonization and the Guidelines for Good Clinical Practice. Written informed consent was obtained from all patients before enrollment.

Study design and treatment

Patients received oral pomalidomide on days 1 to 21 of each 28-day cycle. After completion of the first treatment cycle, patients could choose to continue the study at their assigned pomalidomide dose. Patients who developed PD at any time during pomalidomide treatment or who did not achieve at least minimal response (MR) after completing four cycles—defined as serum and urine M-protein reduction of $\geq 25\%$ and $\geq 50\%$, respectively, compared with baseline—had the option to add oral dexamethasone (40 mg/day on days 1, 8, 15, and 22 of each 28-day cycle) to their current dose level of pomalidomide and could continue treatment until progression. Patients with PD who chose not to add dexamethasone were discontinued from the study.

All patients received aspirin, 81 to 100 mg per day, or another form of thromboprophylaxis. Treatment with bisphosphonates, transfusions of platelets, or red blood cells was permitted at the investigator's discretion. The use of hematopoietic growth factors was permitted after the completion of cycle 1.

Determination of MTD

The primary end point was to determine the MTD of pomalidomide. The first three patients were enrolled in the lowest dose level (2 mg/day) cohort. Following a standard “3+3” design, if one of the first three patients in the 2-mg cohort, or any subsequent dose-level cohort, experienced a dose-limiting toxicity (DLT) within the first cycle and then an additional three patients were to be enrolled into that dose-level cohort. If ≥ 2 patients within the expanded cohort experienced a DLT within the first cycle, then the MTD was considered to have been exceeded and no further dose escalations were needed. If ≤ 1 of the six patients in a dose-level cohort experienced a DLT within the first cycle, then the next cohort of three patients were enrolled at the next highest dose level. Patients who were not evaluable for toxicity were replaced. The MTD was defined as the highest dose level at which ≤ 1 of six patients experienced a DLT within the first 28-day cycle.

DLT was defined as grade 4 neutropenia (ANC $< 500/\mu\text{L}$); febrile neutropenia (fever $\geq 38.5^\circ\text{C}$ and ANC $< 1000/\mu\text{L}$); grade 4 thrombocytopenia (platelet count $< 25\,000/\mu\text{L}$); or grade 3 or 4 pomalidomide-related nonhematologic toxicity. Grade 3 or 4 nausea, vomiting, or diarrhea that could not be controlled using symptomatic treatment was considered a DLT.

Grade 4 transaminitis (serum transaminase $> 20 \times$ ULN) or grade 3 transaminitis (serum transaminase $> 5 \times$ ULN) present for ≥ 7 days was considered a DLT, as was any delay to the start of the second treatment cycle of > 7 days as a result of pomalidomide-related adverse events (AEs). For grade 4 neutropenia occurring after cycle 1, pomalidomide therapy was interrupted and granulocyte colony-stimulating factor (G-CSF) was administered. Pomalidomide was resumed at the start of the next treatment cycle if neutropenia was the only DLT; otherwise, the pomalidomide dose was decreased by one dose level. Use of G-CSF during cycle 1 was not allowed, but was permitted thereafter.

Efficacy and safety assessments

Efficacy assessments were performed every 28 days after completion of the first cycle. Tumor responses, including identification of PD, were determined using modified European Group for Bone Marrow Transplantation criteria^{18,19} and International Myeloma Working Group uniform response criteria.²⁰ Response assessments were based on serum and urine M-protein levels, bone marrow evaluation, and radiographic assessments of lytic bone lesions and/or extramedullary plasmacytoma. Complete blood counts were monitored weekly during cycle 1, biweekly during cycle 2, and then on the first day of each subsequent treatment cycle.

The overall response rate (ORR), time to response, duration of response, and OS were secondary end points. The efficacy analysis was based on both the intent-to-treat (ITT) population, defined as patients who received at least one dose of the study drug, and a subset of efficacy-evaluable population, defined as patients who met the eligibility criteria received at least one dose of the study drug and had a baseline and at least one post-baseline efficacy assessment. The ORR included any patient with at least a confirmed partial response (PR). Time to response was calculated as the time from treatment initiation to the first documented response of at least PR. The duration of response was defined as the time from the response to first evidence of PD. Progression-free survival was also evaluated as part of an exploratory analysis and was defined as the time from treatment initiation to disease progression or death. Overall survival was measured as the time from treatment initiation to death as a result of any cause.

All patients who received at least one dose of pomalidomide were included in the safety analysis. Adverse events were monitored throughout the study and were graded.²¹ Safety and DLTs were summarized at the completion of each dose level and reviewed by the data safety monitoring committee.

Statistical analysis

The standard “3+3” design for dose escalation anticipated enrollment of 6 to 60 patients. Treatment responses are presented as mean (\pm SD) or median values with 95% confidence intervals (CIs). Kaplan-Meier methodology was used to analyze duration of response, PFS, and OS.

Results

Patient characteristics

Thirty-eight patients were enrolled into four pomalidomide dose-level cohorts (Figure 1): 2 mg ($n = 6$); 3 mg ($n = 8$); 4 mg ($n = 14$); and 5 mg ($n = 10$). The baseline characteristics were similar across

Table 1. Patient demographics by dose-level cohort

	Pomalidomide dose levels				
	2 mg (n = 6)	3 mg (n = 8)	4 mg (n = 14)	5 mg (n = 10)	Total (N = 38)
Mean age, years (range)	64.7 (55-72)	70.4 (61-78)	67.5 (45-80)	61.3 (38-83)	66.0 (38-83)
Age ≥75 y, %	0	25	21	10	16
Male, %	17	38	71	40	47
Caucasian, %	83	100	100	80	92
Durie-Salmon stage at enrollment, n (%)					
I	1 (17)	1 (13)	3 (21)	2 (20)	7 (18)
II	0	1 (13)	4 (29)	1 (10)	6 (16)
III	5 (83)	6 (75)	7 (50)	7 (70)	25 (66)
Median duration of active multiple myeloma, years (range)	4.5 (2.8-14.0)	5.9 (2.6-12.0)	5.4 (2.0-23.4)	5.9 (1.4-10.9)	5.5 (1.4-23.4)
Median number of prior therapies, n (range)	7.0 (5-11)	6.5 (2-11)	6.0 (3-17)	5.5 (3-10)	6 (2-17)
Prior lenalidomide and bortezomib, n (%)					
Refractory to lenalidomide	4 (67)	8 (100)	12 (86)	7 (70)	31 (82)
Refractory to lenalidomide as last regimen	1 (17)	3 (38)	5 (36)	2 (20)	11 (29%)
Refractory to bortezomib	3 (50)	7 (88)	10 (71)	8 (80)	28 (74)
Refractory to bortezomib as last regimen	2 (33)	4 (50)	7 (50)	7 (70)	20 (53)
Refractory to both	3 (50)	7 (88)	8 (57)	6 (60)	24 (63)
Prior carfilzomib, n (%)					
Refractory to carfilzomib	3 (50)	3 (38)	4 (29)	2 (20)	12 (32)
Prior dexamethasone, n (%)	6 (100)	8 (100)	14 (100)	10 (100)	38 (100)
Prior thalidomide, n (%)	4 (67)	6 (75)	11 (79)	9 (90)	30 (79)
Prior stem cell transplantation, n (%)	4 (67)	4 (50)	11 (79)	6 (60)	25 (66)

the dose cohorts (Table 1). Patients had received a median of six prior antimyeloma treatments (range, 2 to 17). Sixty-three percent of the patients were refractory to lenalidomide-bortezomib combination treatment.

Determination of MTD and the recommended phase 2 dose

Patients received pomalidomide at dose levels of 2 mg (n = 6), 3 mg (n = 8), 4 mg (n = 14), or 5 mg (n = 10). No DLTs were observed in the first three patients enrolled at the 2-mg dose level. However, one patient discontinued because of thrombocytopenia, and therefore the investigators agreed to enroll three additional patients in this cohort. Only one of the six patients treated with 2 mg experienced a DLT (grade 3 fatigue). No DLTs were initially observed in the 3-mg dose level; however, one patient withdrew because of PD and was replaced by another patient. Of the following three patients enrolled at the 4-mg dose, one had a DLT (grade 4 neutropenia) and the other had renal failure. After four additional patients were enrolled at the 3-mg dose level because of the possibility of two DLTs at the 4-mg dose level, the renal failure experienced by one patient was confirmed to be unrelated to pomalidomide. One of these patients developed a DLT (grade 4 neutropenia). An additional three patients were enrolled at the 4-mg dose level; two of these were not evaluable and were replaced (one withdrew because of PD and one received an incorrect dose of pomalidomide). No additional DLTs were observed

Table 2. Summary of dose-limiting toxicities reported at each pomalidomide dose level

Daily dose of pomalidomide	Median number of completed treatment cycles* (range)	Number of dose-limiting toxicities (type)
2 mg (n = 6)	1.5 (1-12)	1 (grade 3 fatigue)
3 mg (n = 8)	5.0 (2-13)	1 (grade 4 neutropenia)
4 mg (n = 14)	5.5 (1-30)	2 (grade 4 neutropenia)
5 mg (n = 10)	8.0 (1-26)	3 (grade 4 neutropenia)
		1 (grade 3 neutropenia)

*Use of G-CSF was not allowed during the first 28 days (cycle 1) of the phase 1 study.

at 4 mg. Of the next three patients enrolled at the 5-mg dose level, two were not evaluable (1 received radiation therapy and 1 had the dose of pomalidomide reduced to 4 mg because of development of a rash) and were replaced. One DLT was observed (grade 4 neutropenia), so three additional patients were enrolled, one of whom experienced a DLT (grade 3 neutropenia). Although the MTD had been reached at 5 mg, two additional patients had already been enrolled at the 5-mg level, and both patients experienced DLTs (grade 4 neutropenia) before re-trying the 4-mg dose level. Therefore, six patients were enrolled at the 4-mg dose level. One of these patients experienced a DLT (grade 4 neutropenia) so the MTD was determined to be 4 mg.

The DLTs that occurred during the first cycle of treatment are summarized by dose level in Table 2. Overall, eight (21.1%) patients experienced ≥1 DLT. Except for one case of grade 3 fatigue in a patient in the pomalidomide 2-mg cohort, all of the DLTs were grade 4 neutropenia. DLTs were reported in 1, 1, 2, and 4 patients in the 2-mg, 3-mg, 4-mg, and 5-mg cohorts, respectively. All patients in the 5-mg cohort required dose reduction during study treatment. The MTD recommended for the phase 2 dose was, therefore, pomalidomide 4 mg per day for this dosing schedule (namely days 1 to 21 of each 28-day cycle).

Drug exposure and safety

Patients received a median of 5 (range, 1 to 30) cycles of pomalidomide (Table 2). The median duration of treatment with pomalidomide, with or without dexamethasone, was 4.9 months (range, 0.5 to 29). In the 2-mg cohort, the median duration of pomalidomide treatment (1 month) was less than that of the other cohorts (4.5, 5, and 8.1 months in the 3-, 4-, and 5-mg cohorts, respectively). Reasons for early discontinuation in this dose cohort were grade 4 thrombocytopenia (0.5 months), withdrawal of consent (0.5 months), and PD (0.9 months; this patient was included in the efficacy analysis). In total, 13 patients (34.2%) completed ≥9.2 months (40 weeks) of pomalidomide treatment (2-mg cohort [n = 1, 16.7%]; 3-mg cohort [n = 2, 25%]; 4-mg cohort [n = 6, 42.9%]; 5-mg cohort [n = 4, 40%]). Dexamethasone was added in 22 of the 38

Table 3. Treatment-emergent AEs grade 3 or 4 occurring in $\geq 5\%$ of patients across the pomalidomide dosing cohorts

AEs, n (%)	Grade 3 and 4					All Grades
	POM 2 mg (n = 6)	POM 3 mg (n = 8)	POM 4 mg (n = 14)	POM 5 mg (n = 10)	POM Total (N = 38)	POM Total (N = 38)
Neutropenia	1 (17)	4 (50)	7 (50)	8 (80)	20 (53)	23 (61)
Anemia	4 (67)	2 (25)	2 (14)	0	8 (21)	17 (45)
Thrombocytopenia	2 (33)	2 (25)	1 (7)	2 (20)	7 (18)	10 (26)
Sepsis	1 (17)	2 (25)	0	1 (10)	4 (11)	4 (11)
Pneumonia	1 (17)	0	2 (14)	0	3 (8)	5 (13)
Fatigue	2 (33)	1 (13)	2 (14)	1 (10)	6 (16)	27 (66)
Back pain	1 (17)	0	0	1 (10)	2 (5)	8 (21)
Muscle weakness	0	0	2 (14)	0	2 (5)	2 (5)
Renal failure	1 (17)	0	1 (7)	0	2 (5)	2 (5)
DVT	0	0	1 (7)	1 (10)	2 (5)	2 (5)

enrolled patients after a median of 2.8 months. At data cutoff for the phase 1 study (April 1, 2011), four patients were still receiving pomalidomide.

All 38 patients in the phase 1 study experienced ≥ 1 treatment-emergent AEs during treatment. The most commonly reported treatment-emergent AEs (grade 3 or 4) included neutropenia (20 patients, 53%); anemia (8 patients, 21%); thrombocytopenia (7 patients, 18%); and fatigue (6 patients, 16%) (Table 3). G-CSF was administered in 33%, 38%, 36%, and 70% of patients in the 2-, 3-, 4-, and 5-mg cohorts, respectively. Two patients developed grade 3 deep vein thrombosis (DVT) (1 in the 4-mg cohort was receiving dexamethasone and prophylaxis; the other patient was in the 5-mg cohort and was a protocol violation as the patient was not on prophylaxis); PN was reported in 1 patient as a newly emergent event and in four patients who had prior history of PN (only 1 patient had grade 3 PN, and the remainder had grade 1 or 2). There were no cases of febrile neutropenia. There was no relationship between frequency of AEs and pomalidomide dose, with the notable exception of neutropenia (Table 3). There were no unexpected increases in AE frequency after the addition of dexamethasone (data not shown). Overall, 19 patients (50%) had ≥ 1 serious AE (SAE). Five patients (13%) had ≥ 1 SAE attributed to pomalidomide, which included pharyngeal abscess, sepsis, neutropenia, cellulitis, asthenia, musculoskeletal chest pain, atrioventricular block, syncope, and DVT. Dexamethasone-related SAEs occurred in three of the 22 patients (14%) and included infectious arthritis, sepsis, or pharyngeal abscess in two patients and musculoskeletal pain in one patient.

In total, 14 patients (37%) had ≥ 1 dose reduction during treatment. The percentage of patients requiring dose reductions was proportionally related to the dosage of pomalidomide and was 100% in the 5-mg cohort (Table 4). As a result, the median average daily dose of pomalidomide was 2.0, 3.0, 4.0, and 4.4 mg per day in the 2-mg, 3-mg, 4-mg, and 5-mg dose cohorts, respectively. The median time to first dose reduction was 1.3 months (range, 0.3 to 13.8) overall and was not evaluable, and was 1.3, 1.0, and 2.7 months in the 2-mg, 3-mg, 4-mg, and 5-mg dose cohorts, respectively. The main reasons for treatment discontinuation were: disease progression (37%), withdrawal of consent (16%), and AEs (11%); one patient discontinued treatment because of an AE that was suspected to be related to pomalidomide (grade 2 rash).

Efficacy

In total, 38 patients were included in the efficacy analysis based on the (ITT) population (Figure 2A). The ORR was 21%, with a confirmed complete response (CR) in one patient (3%) and PR in

Table 4. Summary of patient disposition and dose reductions/discontinuations related to pomalidomide treatment

n (%)	Pomalidomide dose levels				
	2 mg (n = 6)	3 mg (n = 8)	4 mg (n = 14)	5 mg (n = 10)	Total (N = 38)
Patients active in the study*	0	0	2 (14)	2 (20)	4 (11)
Patients withdrawn from the study	6 (100)	8 (100)	12 (86)	8 (80)	34 (89)
Dose reductions and discontinuations					
POM dose reduction	0	1 (13)	3 (21)	10 (100)	14 (37)
Discontinuation	6 (100)	8 (100)	12 (86)	8 (80)	34 (89)
Disease progression	2 (33)	3 (38)	5 (36)	4 (40)	14 (37)
AEs \S	1 (17)	0	2 (14)	1 (10)	4 (11)
Withdrawn consent	1 (17)	1 (13)	2 (14)	2 (20)	6 (16)
Death	0	1 (13)	2 (14)	0	3 (8)

*As of April 1, 2011.

\S Includes thrombocytopenia, anemia, gastrointestinal hemorrhage, vomiting, chills, fatigue, pyrexia, metastases to meninges, renal failure, and rash.

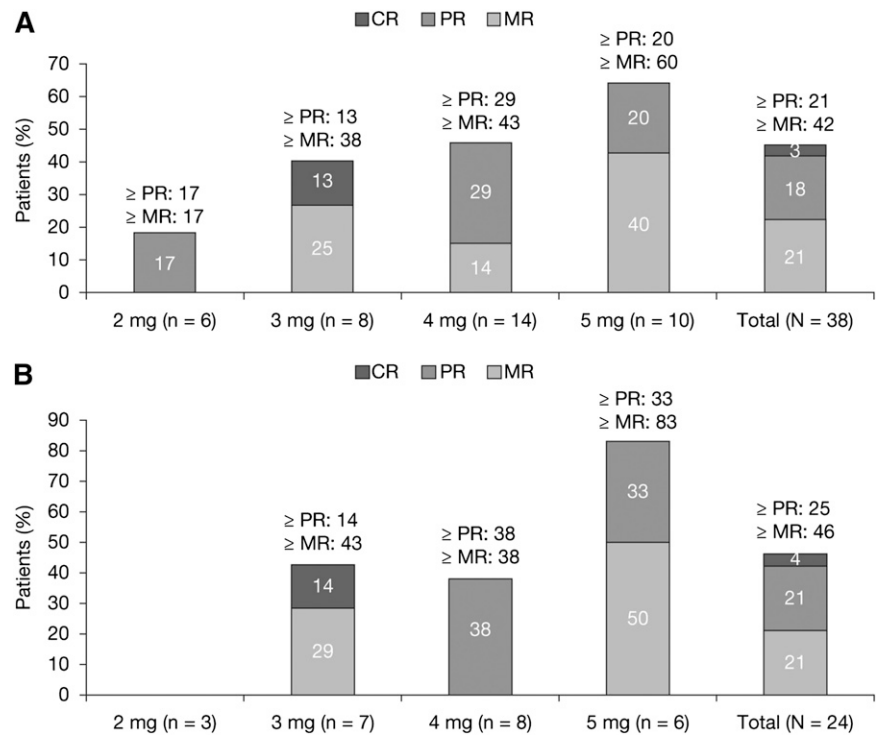
seven patients (18%). MR or better was observed in 42% of the patients, with a trend toward higher response rates with higher pomalidomide dosage (Figure 2A). The median time to response was four months (range, 2 to 26). The best response (\geq PR) to single-agent pomalidomide before the addition of dexamethasone was 13% and an additional eight patients (21%) achieved MR when dexamethasone was added. Overall, 24 patients (63%) were refractory to both lenalidomide and bortezomib, and a confirmed response (at least PR) was seen in six patients (25%; 4% CR) (Figure 2B). In the ITT population, the Kaplan-Meier estimate for the median duration of response was 4.6 months (95% CI, 3.7-13.8). The Kaplan-Meier survival estimates for median PFS and median OS were 4.6 months (95% CI, 2.8-8.3) and 18.3 months (95% CI, 12.3-25.1), respectively.

Efficacy outcomes were similar when the data were analyzed using the efficacy-evaluable population (28 patients). In total, 10 of the 38 patients were not evaluable for efficacy because they did not fulfill the eligibility criteria (n = 5; because of laboratory abnormalities) or had no post-baseline efficacy assessment (n = 5; 3 patients discontinued because of AEs and 2 withdrew consent). In this patient population, CR was reported in 4% of the patients and PR was achieved in 25% of the patients (ORR, 29%). Fifty percent of the patients achieved MR or better. Overall, 22 patients evaluable for response were refractory to both lenalidomide and bortezomib, and a confirmed response (at least PR) was seen in six patients (27%; 5% CR). In the population eligible for response assessment, the Kaplan-Meier estimate for the median duration of response was 4.6 months (95% CI, 3.7-13.8). The Kaplan-Meier survival estimates for median PFS and median OS were 4.6 months (95% CI, 2.8-8.3) and 18.5 months (95% CI, 12.3-25.1), respectively.

Discussion

This phase 1 study used a classic "3+3" design to determine the MTD of oral pomalidomide, which was found to be 4 mg per day when administered as a single agent on days 1 to 21 of a 28-day treatment cycle. All patients treated had RRMM with advanced disease and had received a median of six prior lines of treatment including lenalidomide, bortezomib, thalidomide, and carfilzomib. The most common grade 3 or 4 treatment-emergent AEs included neutropenia, anemia, thrombocytopenia, and fatigue. The rate of grade 3 or 4

Figure 2. Treatment responses to pomalidomide in patients with RRMM. (A) ITT population (N = 38). (B) Dual lenalidomide and bortezomib–refractory patients (N = 24).



neutropenia in this study was 53%, consistent with a previous study in RRMM, in which pomalidomide 4 mg per day was used (albeit using a different dose schedule),⁵ and was equivalent to rates reported with lenalidomide monotherapy in a similar population.^{22,23} The incidence of grade 3 or 4 thromboembolic events in the current study was low (5%) and also comparable with previous studies with single-agent lenalidomide.²³ The low incidence of treatment-emergent PN is noteworthy because the patients in this study had received multiple lines of prior therapy, including bortezomib and thalidomide, both of which are commonly associated with neurotoxicity.²⁴⁻²⁶ Discontinuations because of AEs were uncommon, allowing patients to receive therapy consistently and continuously until disease progression.

In our study, pomalidomide, with or without dexamethasone (40 mg per week) was associated with an ORR of 21% (29% for the efficacy-evaluable population, including 3% CR, 4% for the efficacy-evaluable population) and a ≥MR rate of 42% (50% for the efficacy-evaluable population) in patients with RRMM who had received multiple lines of prior therapy. This promising clinical activity is consistent with previous phase 2 studies of pomalidomide.^{2,5,16,27} Specifically, pomalidomide plus low-dose dexamethasone has demonstrated overall response rates (CR + very good PR [VGPR] + PR) of 63% in patients with relapsed MM (<3 prior regimens),² 32% in patients refractory to lenalidomide (median of 4 lines of treatment),¹⁶ and up to 29% in heavily pretreated patients who had received prior thalidomide and were refractory to both lenalidomide and bortezomib (median of 6 lines of treatment).⁵ Interestingly, in contrast to the latter study,⁵ our data suggest a dose-dependent response to pomalidomide, with higher response rates in patients who had received higher doses of pomalidomide. Importantly, in dual-refractory patients in the study of Lacy et al,⁵ duration of response appeared to be dose dependent, supporting our observation. However, the patient cohorts in both of these studies were small, and therefore evaluation of the dose response in larger numbers of patients is warranted.

Responses to pomalidomide, generally in combination with dexamethasone (40 mg per week), were durable (median response

duration 4.6 months in both the ITT and the efficacy-evaluable population). The median PFS was also 4.6 months for both populations, and the median OS was 18.3 months in the ITT population and 18.5 months in the efficacy-evaluable population. The survival outcomes observed in the current study are encouraging and compare favorably with data with another second generation novel agent, carfilzomib, tested in a similar population of RRMM patients.²⁷ However, although very encouraging, these results with pomalidomide (with or without dexamethasone) are still preliminary and require further exploration in larger phase 2 trials.

Outcomes with the dosing schedule studied here are also comparable with other previously reported outcomes for pomalidomide, with or without dexamethasone, where median PFS ranged from 3.2 to 11.6 months and median OS ranged from 13.9 to 20.7 months.^{2,5,14,16} Interestingly, the IFM 2009-02 phase 2 trial compared two schedules of pomalidomide plus low-dose dexamethasone in patients refractory to lenalidomide and bortezomib, either 4 mg per day on days 1 to 21 of each 28-day cycle (21/28) or 4 mg per day each day of the 28-day cycle (28/28). PR or better was reported in 42% and 39% of patients, for the 21 of 28-day and 28 of 28-day dosing regimens, respectively, with a longer duration of response and less toxicity for the 21 of 28-day schedule, but comparable 6-month survival rates of 88% and 85%, respectively.¹⁷ A similar, encouraging 2-year survival rate of 76% has recently been reported in patients with RRMM treated with pomalidomide and low-dose dexamethasone.²⁸ The safety profiles of pomalidomide and low-dose dexamethasone combination therapy in three other phase 1 and 2 clinical trials were also comparable with the current study.^{5,15,16}

The results of this phase 1 study show that pomalidomide, given at 4 mg per day on days 1 to 21 of each 28-day cycle in combination with dexamethasone 40 mg per week, is associated with encouraging response rates and manageable safety in patients with RRMM

previously treated with lenalidomide and bortezomib. Pomalidomide, administered at a dose of 4 mg per day on days 1 to 21 of each 28-day cycle is being evaluated in ongoing phase 2 and 3 trials. Larger studies are required to further confirm the role of pomalidomide in patients with RRMM, both in combination with dexamethasone and with other novel agents, such as bortezomib.^{29,30}

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References

- Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520.
- Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *J Clin Oncol*. 2009;27(30):5008-5014.
- Kumar SK, Lee JH, Lahuerta JJ, et al. International Myeloma Working Group. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia*. 2012;26(1):149-157.
- Sinha S, Lacy M, Mikhael J, et al. Response to salvage therapies and outcome in patients with multiple myeloma relapsing after pomalidomide therapy. *Leukemia*. 2012;26(4):839-841.
- Lacy MQ, Allred JB, Gertz MA, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. *Blood*. 2011;118(11):2970-2975.
- Corral LG, Haslett PA, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J Immunol*. 1999;163(1):380-386.
- Verhelle D, Corral LG, Wong K, et al. Lenalidomide and CC-4047 inhibit the proliferation of malignant B cells while expanding normal CD34+ progenitor cells. *Cancer Res*. 2007;67(2):746-755.
- 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(9):2943-2950.
- Escoubet-Lozach L, Lin IL, Jensen-Pergakes K, et al. Pomalidomide and lenalidomide induce p21 WAF-1 expression in both lymphoma and multiple myeloma through a LSD1-mediated epigenetic mechanism. *Cancer Res*. 2009;69(18):7347-7356.
- Gandhi AK, Kang J, Capone L, et al. Dexamethasone synergizes with lenalidomide to inhibit multiple myeloma tumor growth, but reduces lenalidomide-induced immunomodulation of T and NK cell function. *Curr Cancer Drug Targets*. 2010;10(2):155-167.
- Görgün G, Calabrese E, Soydan E, et al. Immunomodulatory effects of lenalidomide and pomalidomide on interaction of tumor and bone marrow accessory cells in multiple myeloma. *Blood*. 2010;116(17):3227-3237.
- 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(12):4525-4530.
- Ryback L, Mendy D, Miller K, et al. Overcoming resistance; the use of pomalidomide and dexamethasone in re-sensitizing lenalidomide-resistant multiple myeloma cells. *Haematologica*. 2011;96(S1):abstr P328.
- Schey SA, Fields P, Bartlett JB, et al. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J Clin Oncol*. 2004;22(16):3269-3276.
- Streety MJ, Gyertson K, Daniel Y, et al. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation. *Br J Haematol*. 2008;141(1):41-51.
- Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). *Leukemia*. 2010;24(11):1934-1939.
- Leleu Y, Attal M, Arnulf B, et al. Phase 2 multicenter, randomized, open-label study of 2 modalities of pomalidomide plus low-dose dexamethasone (POMD) in patients with multiple myeloma (MM), refractory to both lenalidomide and bortezomib (double refractory), IFM 2009-02. *Haematologica*. 2011;96(S1): abstr P148.
- Bladé J, Samson D, Reece D, et al. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. *Br J Haematol*. 1998;102(5):1115-1123.
- Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med*. 2003;348(26):2609-2617.
- Durie BG, Harousseau JL, Miguel JS, et al. International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467-1473.

Authorship

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21. National Cancer Institute Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events. version 3.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf
22. 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(10):3458-3464.
23. Richardson P, Jagannath S, Hussein M, et al. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. *Blood*. 2009;114(4):772-778.
24. Richardson PG, Briemberg H, Jagannath S, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *J Clin Oncol*. 2006;24(19):3113-3120.
25. Richardson PG, Sonneveld P, Schuster MW, et al. Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline. *Br J Haematol*. 2009;144(6):895-903.
26. Richardson P, Schlossman R, Jagannath S, et al. Thalidomide for patients with relapsed multiple myeloma after high-dose chemotherapy and stem cell transplantation: results of an open-label multicenter phase 2 study of efficacy, toxicity, and biological activity. *Mayo Clin Proc*. 2004;79(7): 875-882.
27. Siegel DSD, Martin T, Wang M, et al. PX-171-003-A1, an open-label, single-arm, phase (Ph) II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (R/R MM): Long-term follow-up and subgroup analysis. *J Clin Oncol*. 2011;29: abstr 8027.
28. Mikhael J, Gertz M, Hayman S, et al. Long-term efficacy and duration of response of pomalidomide in patients with relapsed multiple myeloma. *Haematologica*. 2011;96(S1):abstr P300.
29. Richardson PG, Mitsiades C, Schlossman R, et al. New drugs for myeloma. *Oncologist*. 2007; 12(6):664-689.
30. Richardson PG, Weller E, Jagannath S, et al. Multicenter, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and relapsed/refractory multiple myeloma. *J Clin Oncol*. 2009;27(34):5713-5719.