Final Results From the Phase 1b/2 Study (PX-171-006) of Carfilzomib, Lenalidomide, and Low-dose Dexamethasone (CRd) in Patients With Relapsed or Progressive Multiple Myeloma

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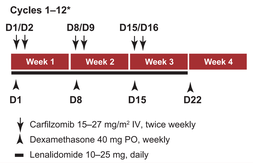
Introduction

- Carfilzomib is a selective proteasome inhibitor approved in the United States as a single-agent treatment for patients with relapsed and refractory multiple myeloma (RRMM).[1,2]
- PX-171-006 is a phase 1b/2 study to evaluate the safety and efficacy of carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRd) in patients with relapsed or progressive MM.
  - Results from the phase 1b dose-escalation portion of the study have recently been reported,[3] and the phase 2 dose-expansion portion was subsequently initiated at the maximum planned dose (MPD) of CRd.
- Herein, we present final efficacy and safety results of the overall study population and the MPD cohort.

Patients and Methods

- PX-171-006 was a multicenter, single-arm, open-label phase 1b/2 study (NCT00603447).
- Patients with symptomatic and measurable MM and evidence of relapsed or progressive disease (PD) after 1–3 prior lines of therapy were eligible, provided they had achieved at least a minimal response (MR) to a prior therapy.
- Patients were treated with CRd in 28-day cycles (**Figure 1**). At the MPD, carfilzomib was given intravenously as a 2- to 10-min infusion on Days 1, 2, 8, 9, 15, and 16 at a dose of 20 mg/m^2 on Days 1 and 2 and 27 mg/m^2 thereafter. Lenalidomide was dosed orally at 25 mg/day on Days 1–21. Oral dexamethasone (40 mg) was given once weekly.
- The primary endpoint of the phase 1b portion of the trial was safety and the determination of the maximum tolerated dose (MTD) or MPD. Secondary endpoints for the phase 1b/2 included overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS).
- Disease response was defined according to the International Myeloma Working Group (IMWG) guidelines with the addition of MR defined per European Blood and Marrow Transplantation Group (EBMT).[4,5] Response was assessed on Day 15 of Cycle 1 and on Day 1 of all subsequent cycles.

Figure 1. Dosing schedule (28-day cycle)



Cohort	Carfilzomib mg/m^2	Lenalidomide mg
1	15	10
2	15	15
3	15	20
4	20	20
5	20	25
6/7 (MPD)	20/27†	25

D, day; IV, intravenous, MPD, maximum planned dose, PO, orally
*Cycles 13–18 (maintenance) carfilzomib dosing modified to Days 1, 2, 15, 16.
†20 mg/m^2 Days 1 and 2 during Cycle 1; 27 mg/m^2 thereafter.

Results

- The study was initiated in June 2008 and enrollment was completed in February 2010. The date of data cut-off was April 18, 2013.
- A total of 84 patients with relapsed or progressive MM were enrolled—40 in the phase 1b portion (8 treated at the MPD) and 44 in the phase 2 dose-expansion portion (all 44 treated at the MPD).
- Patient demographics and disease characteristics are shown in **Table 1**; 20.2% of patients were refractory to bortezomib and 34.5% were refractory to lenalidomide. For the MPD cohort, 26.9% were refractory to bortezomib and 42.3% were refractory to lenalidomide.
- In the overall study population, 70.2% of patients had received bortezomib and an immunomodulatory agent, either in combination or in separate regimens (**Table 2**).
- All 84 patients were evaluable for response. Three patients (3.6%) remained on treatment at the time of data cut-off.

Table 1. Baseline Characteristics

	MPD Cohort (N=52)	Overall (N=84)
Age, years, median (range)	63.0 (44–86)	61.5 (43–86)
Male, n (%)	31 (59.6)	48 (57.1)
ECOG performance status, n (%)		
0	25 (48.1)	33 (39.3)
1	23 (44.2)	46 (54.8)
2	4 (7.7)	5 (6.0)
Time since diagnosis, years, median (range)*	3.1 (0–16)	3.1 (0–22)
International Staging System, n (%)		
I	20 (38.5)	35 (41.7)
II/III	30 (57.7)	46 (54.8)
Cytogenetics/FISH		
Standard-risk	40 (76.9)	57 (67.9)
High-risk	11 (21.2)	22 (26.2)
Refractory disease, n (%)†		
Last regimen	21 (40.4)	34 (40.5)
Bortezomib	14 (26.9)	17 (20.2)
Lenalidomide	22 (42.3)	29 (34.5)
Bortezomib and lenalidomide	7 (13.5)	8 (9.5)

ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; MPD, maximum planned dose
*Data unavailable for 1 patient; †≤25% response or progression during therapy.

Table 2. Prior Therapies

	MPD Cohort (N=52)	Overall (N=84)
Prior lines of therapy, median (range)	3 (1–5)	2 (1–5)
Prior therapy, n (%)*		
Corticosteroid	50 (96.2)	82 (97.6)
Bortezomib	42 (80.8)	65 (77.4)
Lenalidomide	38 (73.1)	59 (70.2)
Thalidomide	24 (46.2)	39 (46.4)
Bortezomib and lenalidomide	31 (59.6)	49 (58.3)
Bortezomib and lenalidomide or thalidomide	38 (73.1)	59 (70.2)
Alkylating agent	37 (71.2)	61 (72.6)
Anthracycline	20 (38.5)	29 (34.5)
Transplant	29 (55.8)	54 (64.3)

*Exposure to multiple drugs was not necessarily concurrent.

Efficacy

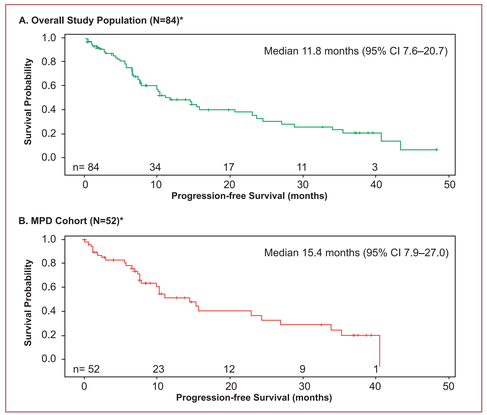
- ORR (≥ PR) was 69.0% overall and 76.9% for the MPD cohort (**Table 3**).
- Median DOR was 18.8 months overall and 22.1 months for the MPD cohort.
- The median time to ≥ PR was 1.0 month for the overall and MPD cohorts.
- With a median follow-up of 32.7 months, the median PFS was 11.8 months overall and 15.4 months for the MPD cohort (**Figure 2**).
- In patients refractory to lenalidomide overall (**Table 4**), the ORR was 58.6%, the median DOR was 13.8 months (95% CI 6.5–NE), and the median PFS was 9.9 months (95% CI 5.6–24.4).
- In patients who were lenalidomide-naïve overall, the ORR was 80%, median DOR was 21.4 months (95% CI 21.1–41.5), and median PFS was 28.7 months (95% CI 23.7–43.4).

Table 3. Response Results

	MPD Cohort (N=52)	Overall (N=84)
Best response, n (%)		
Stringent complete response	2 (3.8)	3 (3.6)
Complete response	1 (1.9)	1 (1.2)
Very good partial response	19 (36.5)	30 (35.7)
Partial response	18 (34.6)	24 (28.6)
Minimal response	0 (0)	5 (6.0)
Stable disease	3 (5.8)	7 (8.3)
Progressive disease	5 (9.6)	6 (7.1)
Not evaluable	4 (7.7)	8 (9.5)
Overall response rate, n (%)*	40 (76.9)	58 (69.0)
Median time to response, months (range)	1.0 (0–5)	1.0 (0–30)
Median duration, months (95% CI)†	22.1 (9.5–35.0)	18.8 (9.7–25.1)

*Partial response or better; †Estimated by the Kaplan-Meier method.

Figure 2. Progression-free Survival



*Seven patients overall and 6 in the MPD cohort opted to discontinue treatment after achieving at least a PR and prior PD in order to pursue alternate therapies (eg, autologous stem cell transplantation [ASCT]).

Table 4. Efficacy Results by Subgroup

	Lenalidomide Naïve		Lenalidomide Refractory		Bortezomib Refractory	
	MPD n=14	Overall N=25	MPD n=22	Overall N=29	MPD n=14	Overall N=17
ORR, n (%)	12 (85.7)	20 (80.0)	15 (68.2)	17 (58.6)	10 (71.4)	10 (58.8)
Median DOR (95% CI), months	NE (5.3–NE)	21.4 (21.1–41.5)	23.5 (6.1–NE)	13.8 (6.5–NE)	18.5 (5.8–25.1)	18.5 (5.8–25.1)
Median PFS (95% CI), months	NE (7.3–NE)	28.7 (23.7–43.4)	9.9 (5.6–34.1)	9.9 (5.6–24.4)	12.9 (1.2–24.4)	9.9 (1.2–23.1)

DOR, duration of response; MPD, maximum planned dose; NE, not estimable; ORR, overall response rate; PFS, progression-free survival

Safety

- The most common hematologic adverse events (AEs) are summarized in **Table 5**; non-hematologic AEs are summarized in **Table 6**.
- In the overall study population, 33.3% of patients completed more than 12 cycles of CRd and 21.4% completed more than 18 cycles; corresponding values in the MPD cohort were 36.5% and 25.0%, respectively.
- In the overall study population:
  - The median number of carfilzomib cycles started was 8.5 (range 1–53). 20.2% discontinued CRd due to an AE; 48.8% due to PD (**Table 7**); 4.8% required carfilzomib dose reductions due to AEs.
  - The most common AEs of any Grade were fatigue (65.5%), diarrhea (56.0%), and neutropenia (45.2%).
  - Grade 3/4 AEs were generally hematologic in nature and included neutropenia (36.9%), lymphopenia (31.0%), and thrombocytopenia (25.0%).
  - Peripheral neuropathy occurred in 18 patients (21.4%), with only 1 patient (1.2%) experiencing a Grade 3 event and no Grade 4 events.
  - Three deaths occurred during or within 30 days of treatment discontinuation, with progressive disease the primary cause of death in all 3. In 1 of these patients, a secondary cause of death (colonic stenosis) was deemed possibly related to study treatment by the investigator.
- The safety and tolerability profile in the MPD cohort was consistent with the overall results.

Table 5. Treatment-emergent Hematologic AEs Occurring in ≥25% of Patients for Any Grade or ≥5% for Grade 3/4

	MPD Cohort (N=52)		Overall (N=84)	
	Any Grade, n (%)	Grade 3/4 n (%)	Any Grade, n (%)	Grade 3/4 n (%)
Neutropenia	19 (36.5)	16 (30.8)	38 (45.2)	31 (36.9)
Anemia	17 (32.7)	9 (17.3)	32 (38.1)	15 (17.9)
Thrombocytopenia	16 (30.8)	10 (19.2)	29 (34.5)	21 (25.0)
Lymphopenia	21 (40.4)	19 (36.5)	28 (33.3)	26 (31.0)
Leukopenia	10 (19.2)	4 (7.7)	16 (19.0)	9 (10.7)

Table 6. Treatment-emergent Non-hematologic AEs Occurring in ≥25% of Patients for Any Grade or ≥5% for Grade 3/4

	MPD Cohort (N=52)		Overall (N=84)	
	Any Grade, n (%)	Grade 3/4 n (%)	Any Grade, n (%)	Grade 3/4 n (%)
Fatigue	36 (69.2)	6 (11.5)	55 (65.5)	6 (7.1)
Diarrhea	30 (57.7)	3 (5.8)	47 (56.0)	5 (6.0)
Cough	21 (40.4)	1 (1.9)	35 (41.7)	1 (1.2)
Upper respiratory tract infection	23 (44.2)	1 (1.9)	34 (40.5)	2 (2.4)
Pyrexia	23 (44.2)	0 (0.0)	33 (39.3)	0 (0.0)
Muscle spasm	20 (38.5)	2 (3.8)	30 (35.7)	2 (2.4)
Dyspnea	18 (34.6)	0 (0.0)	29 (34.5)	1 (1.2)
Peripheral edema	19 (36.5)	0 (0.0)	28 (33.3)	1 (1.2)
Back pain	16 (30.8)	1 (1.9)	27 (32.1)	2 (2.4)
Insomnia	18 (34.6)	0 (0.0)	26 (31.0)	0 (0.0)
Nausea	17 (32.7)	0 (0.0)	25 (29.8)	0 (0.0)
Hypophosphatemia	20 (38.5)	13 (25.0)	24 (28.6)	17 (20.2)
Hyperglycemia	14 (26.9)	4 (7.7)	23 (27.4)	11 (13.1)
Constipation	13 (25.0)	0 (0.0)	21 (25.0)	0 (0.0)
Hypokalemia	12 (23.1)	4 (7.7)	21 (25.0)	7 (8.3)
Pain in extremity	13 (25.0)	0 (0.0)	21 (25.0)	0 (0.0)
Hyponatremia	8 (15.4)	5 (9.6)	14 (16.7)	9 (10.7)
Pneumonia	9 (17.3)	6 (11.5)	14 (16.7)	8 (9.5)

Table 7. Reasons for Discontinuation

	MPD Cohort (N=52)	Overall (N=84)
Reason CRd discontinued, n (%)		
Progressive Disease	24 (46.2)	41 (48.8)
Adverse Event	12 (23.1)	17 (20.2)
Withdrew Consent	1 (1.9)	4 (4.8)
Completed treatment per protocol	–	2 (2.4)
Other*	13 (25.0)	17 (20.2)

*Includes patient/physician preference, patients proceeding to stem cell collection/transplantation or maintenance therapy, and non-compliance

Conclusions

- CRd treatment provided robust, rapid, and durable responses in patients with relapsed or progressive MM, including the 35% of the patients in the overall population who were refractory to lenalidomide.
  - Notably, median PFS in the 30% of lenalidomide-naïve overall patients was 28.7 months.
  - Response and safety data in the 20/27 mg/m^2 MPD cohort compared favorably with the overall study population.
- CRd had an acceptable safety and tolerability profile in this patient population with infrequent carfilzomib dose reductions and Grade 3 peripheral neuropathy and moderate rates of discontinuation due to AEs.
- Additional studies are ongoing evaluating the CRd regimen including the phase 3 ASPIRE study (NCT01080391) in relapsed MM[6] and several phase 2 studies in NDMM.[7,8]

Disclosures

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