

# An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib

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Multiple myeloma (MM) will affect an estimated 21 700 people and cause over 10 710 deaths in the United States (US) in 2012 [American Cancer Society ACS (2012)]. The US 5-year relative survival rate from 1999 to 2006 was just 39%, with a median survival of 4 years (Rajkumar, 2009; Siegel *et al*, 2011a). Previously, therapy for relapsed and/or

## Summary

Carfilzomib is a next-generation proteasome inhibitor that selectively and irreversibly binds to its target. In clinical studies, carfilzomib has shown efficacy in patients with relapsed and/or refractory multiple myeloma (MM) and has demonstrated a tolerable safety profile. In this phase 2, open-label, multicentre clinical trial, 35 patients with relapsed and/or refractory MM following 1–3 prior therapies, including at least one bortezomib-based regimen, received carfilzomib 20 mg/m<sup>2</sup> in a twice-weekly, consecutive-day dosing schedule for ≤ 12 monthly cycles. The best overall response rate (ORR) was 17.1% and the clinical benefit response rate (ORR + minimal response) was 31.4%. The median duration of response was >10.6 months and the median time to progression was 4.6 months. The most common adverse events were fatigue (62.9%), nausea (60.0%), and vomiting (42.9%). No exacerbation of baseline peripheral neuropathy was observed. Single-agent carfilzomib was generally well tolerated for up to 12 treatment cycles and showed activity in patients with relapsed and/or refractory MM who had received prior treatment with bortezomib. These data, combined with an acceptable toxicity profile, support the potential use of carfilzomib in patients with relapsed and/or refractory MM and warrant continued investigation of carfilzomib as single agent or in combination with other agents.

**Keywords:** Multiple myeloma, proteasome inhibitor, relapsed, refractory, phase 2.

refractory MM (i.e., patients who are either relapsed and refractory OR relapsed or refractory) consisted primarily of combination therapies based around melphalan, prednisone, cyclophosphamide, dexamethasone or other broadly cytotoxic agents (Kyle & Rajkumar, 2008); however, treatment options and corresponding patient outcomes have

greatly improved in the past decade following the introduction of agents, such as thalidomide, lenalidomide and liposomal doxorubicin (Plosker, 2008; Rajkumar, 2009; Laubach *et al*, 2010). One notable therapy that has emerged in recent years has been the proteasome inhibitor bortezomib (Velcade<sup>®</sup>, Millennium Pharmaceuticals, Cambridge, MA, USA), the first-in-class drug that validated the proteasome as a target for therapeutic approaches to MM (Hideshima *et al*, 2001; Kane *et al*, 2003). Proteasome inhibitors such as bortezomib are effective anti-cancer agents, as transformed cells generally have a higher level of proteasome activity than differentiated cells (Kanayama *et al*, 1991).

Although it is effective as an anti-myeloma drug, there are limitations to the use of bortezomib, including development of resistance and painful peripheral neuropathy (Mohty *et al*, 2010; Boyette-Davis *et al*, 2011). These adverse effects of bortezomib have limited its use in some patients, for whom there is a need for additional treatment options. A number of modifications to the clinical dosing scheme for bortezomib (eg, weekly dosing, subcutaneous (SC) administration) have been evaluated in an effort to address these issues, with encouraging results (Brinthen *et al*, 2010; Moreau *et al*, 2011). However, there is still a need for a next generation of proteasome inhibitors with greater efficacy and improved tolerability profiles. One such novel proteasome inhibitor currently under development is carfilzomib (formerly PR-171; Onyx Pharmaceuticals, South San Francisco, CA, USA).

Carfilzomib is a potent and highly selective proteasome inhibitor that is structurally and mechanistically distinct from bortezomib (Demo *et al*, 2007). Carfilzomib selectively and irreversibly inhibits the chymotrypsin-like activity of the 20S proteasome, necessitating *de novo* protein synthesis to restore activity (Parlati *et al*, 2009). In preclinical studies, carfilzomib demonstrated more potent proteasome inhibition and minimal off-target activity against non-proteasomal proteases relative to bortezomib (Demo *et al*, 2007). In addition, consecutive-day dosing of carfilzomib was well-tolerated and led to prolonged irreversible proteasome inhibition (Demo *et al*, 2007). Carfilzomib has also shown a lack of histological or behavioural neurotoxicity with chronic dosing in animals (Kirk *et al*, 2008; Arastu-Kapur *et al*, 2011) and displayed cytotoxic activity against bortezomib-resistant cell lines (Kuhn *et al*, 2007).

Early clinical studies testing carfilzomib in patients with relapsed and/or refractory haematological malignancies including MM have been encouraging, with rapid responses beginning shortly after the onset of therapy, primarily mild or moderate haematological toxicities, and low rates of peripheral neuropathy (PN) (Alsina *et al*, 2007; O'Connor *et al*, 2009; Singhal *et al*, 2011). A minimal effective dose of 15 mg/m<sup>2</sup> has been established. (O'Connor *et al*, 2009). Durable responses (from >90 to >280 d) have been achieved in patients using a twice-weekly, consecutive-day dosing schedule, and responses were observed in patients who had failed bortezomib therapy, treatment with immunomodulatory agents, and stem cell transplant (Alsina *et al*, 2007).

Following these promising results, 2 phase 2 studies were initiated to evaluate single-agent carfilzomib in patients with relapsed and refractory MM following at least two lines of therapy (PX-171-003) and in patients with relapsed and/or refractory MM following 1–3 prior therapies (PX-171-004). The 003 study, from which the results have been submitted to the US Food and Drug Administration for regulatory review and accelerated approval of carfilzomib, involved a larger population of patients ( $N = 266$ ) (Siegel *et al*, 2010). The 004 study is a smaller study originally designed to investigate the impact of carfilzomib treatment in less heavily-treated patients. The results presented here are from the analysis of the lower dose, first cohort of a larger study in patients who had previously been exposed to bortezomib (Fig 1). Following an amendment to the study, a separate cohort that included only bortezomib-naïve patients was initiated to investigate a higher dose of carfilzomib; the data for bortezomib-naïve patients were analysed independently and published separately (Vij *et al*, 2012).

## Methods

### Study design and eligibility

This was a phase 2 multicentre, open-label, single-arm study registered at ClinicalTrials.gov (NCT00530816). Written informed consent was obtained from all enrolled patients in accordance with the Declaration of Helsinki, and the study was approved by the Institutional Review Board of each participating centre.

Patients with measurable relapsed and/or refractory MM who were 18 years of age or older were eligible to participate in this study. Measurable disease was defined as either or both of the following: serum M-protein  $\geq 10$  g/l and/or urine M-protein  $\geq 200$  mg/24 h. Prior to an amendment to

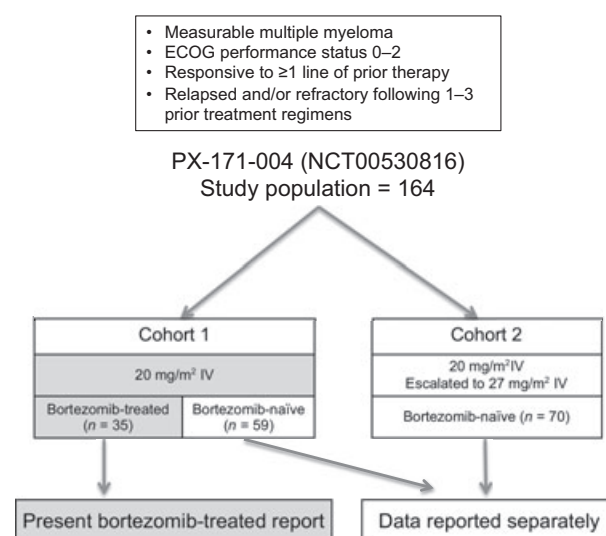


Fig 1. PX-171-004 Study Design. ECOG, Eastern Cooperative Oncology Group.

the protocol, four patients were permitted to enter the study with disease measurable by serum free light chain (sFLC) only. Key inclusion criteria were: Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2, responsive [i.e., achieved minimal response (MR) or better] to standard first-line therapy, and relapsed or relapsed and refractory after 1–3 prior therapeutic regimens (including at least one bortezomib-containing regimen). Refractory disease was defined as  $\leq 25\%$  response or progressive disease (PD) either during therapy or within 60 d after completion of the last therapy. Induction therapy, stem cell transplant, and planned maintenance were considered as one regimen. Patients were also required to have: total white blood cell (WBC) count  $\geq 2.0 \times 10^9/l$ , absolute neutrophil count (ANC)  $\geq 1.0 \times 10^9/l$ , haemoglobin  $\geq 80$  g/l, platelet count  $\geq 50 \times 10^9/l$ , creatinine clearance (CrCl)  $\geq 30$  ml/min, and adequate hepatic function.

Excluded from the study were patients who: had received glucocorticoid therapy (prednisone  $>10$  mg/d or equivalent) or chemotherapy with an approved or investigational anticancer treatment (including corticosteroid therapy) within the 3 weeks prior to first dose; received radiation therapy or immunotherapy in the 4 weeks prior to first dose or received localized radiation therapy within 1 week prior to first dose; participated in an investigational therapeutic study within 3 weeks or 5 drug half-lives prior to first dose (whichever time was greater); or had prior treatment with carfilzomib. Other exclusion criteria included cardiovascular disease (including congestive heart failure [New York Heart Association Grade III or IV], symptomatic ischaemia, uncontrolled conduction abnormalities, and myocardial infarction); acute active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks prior to first dose; human immunodeficiency virus seropositivity or active hepatitis A, B, or C infection; or significant neuropathy (Grade 3, 4, or Grade 2 with pain) at the time of the study initiation.

### Treatment

Intravenous (IV) carfilzomib ( $20$  mg/m<sup>2</sup>) was administered over a period of 2–10 min on days 1, 2, 8, 9, 15, and 16 of every 28-d cycle for up to 12 cycles. During the first cycle, prophylactic dexamethasone at a dose of 4 mg/d was administered prior to each dose of carfilzomib to ameliorate fever, chills, shortness of breath, and/or rigors. In phase 1 studies, these symptoms had been observed in small subsets of study patients in Cycle 1 and occasionally in Cycle 2. In the current study, if any of these treatment-related effects were observed during treatment after dexamethasone had been discontinued, oral (PO) or IV dexamethasone 4 mg was permitted to be re-administered prior to subsequent doses of carfilzomib. Carfilzomib doses were held or reduced to 15 and 11 mg/m<sup>2</sup> in response to certain adverse events (AEs), and following resolution, patients were permitted to resume treatment at the same dose level (eg, for reversible haemato-

logical AEs) or a reduced dose level, depending on the AE. No more than 2 dose reductions were permitted before removal from the study. Patients completing 12 cycles of treatment with carfilzomib were eligible to continue receiving carfilzomib on extension study PX-171-010 (NCT00884312).

### Assessment of response and safety

The response-evaluable population comprised patients who had completed at least one cycle of treatment with carfilzomib, underwent at least one post-baseline response assessment, and had disease measurable by protein electrophoresis. Overall response rate (ORR) to carfilzomib included stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR). The primary endpoint of ORR was based on response-evaluable subset population, which excluded four patients whose disease was followed by sFLC measurement only. Secondary endpoints were based on the whole response-evaluable population and included: the best ORR throughout the treatment period and clinical benefit response (CBR) rate (ORR + MR); duration of response (DOR), defined as time from first evidence of PR or better, i.e., first observation of PR that is subsequently confirmed to PD or death without PD; time to progression (TTP), defined as time from study entry (first dose of carfilzomib) to PD; and overall survival (OS, defined as time from first dose of carfilzomib to date of death). Progression-free survival (PFS, defined as time from start of treatment to PD or death due to any cause) was also included. Additional exploratory efficacy endpoints were duration of clinical benefit (defined as the time from first confirmed MR or higher to the first confirmed PD or death without PD) and duration of MR.

Patients were evaluated for response on Day 15 of Cycle 1, Day 1 of Cycles 2–12, and at the end of the study. Responses and progression were assessed according to the International Myeloma Working Group's Uniform Response Criteria (Durie *et al*, 2006) for all except MR, which was assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria (Blade *et al*, 1998). In brief, MR was defined in the protocol as reduction of M-protein  $\geq 25\%$  and  $<50\%$  in serum or  $\geq 50\%$  and  $<90\%$  in urine, maintained for 6 weeks (MR was considered confirmed with an interval of at least 4 weeks between measurements for patients with an observation of PD or death at least 6 weeks from the first MR observation). Responses were reviewed, confirmed, and adjudicated by an independent review committee consisting of four individuals not associated with the trial (three clinicians as voting members and one non-voting secretary). Independent Review Committee (IRC) assessments were documented in the case report form (CRF) and entered in a database maintained separately from the clinical database. Discordant cases between the IRC and investigator were re-reviewed by the IRC, which was also documented in the CRF.

The incidence and severity of AEs were also assessed. The safety population included all patients who received at least one dose of carfilzomib. Safety assessments included AEs and serious AEs (SAEs), laboratory values, and vital signs. AEs were summarized based on the number and percentage of patients experiencing events according to the Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>, Chantilly, VA, USA) AE dictionary system organ class and preferred term. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 ([http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf)), was used to grade AEs.

Because of the significant rates of PN historically observed with the use of bortezomib, the incidence and severity of PN was carefully evaluated in this study. Detailed individual neuropathy histories were collected at screening, and comprehensive neurophysical examinations were conducted. In addition, patients were required to complete a PN-related quality of life (QoL) survey, the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTx) version 4.0 (Huang *et al*, 2007). Following every two cycles of treatment, neurological exams were conducted and patients completed the FACT-GOG/NTx questionnaire.

### Statistical analyses

Descriptive statistics, including 2-sided 95% confidence intervals (CIs), were used to summarize all study endpoints. All statistical analyses were performed using SAS<sup>®</sup> version 9.1 or later (SAS Institute, Inc., Cary, NC, USA). Best ORR was determined based on a 2-sided 95% CI for evaluable patients whose best response was classified as sCR, CR, VGPR, or PR.

Analysis of ORR was performed in subgroups defined according to a number of covariates as exploratory analyses by patient baseline characteristics of age, ECOG PS, International Staging System (ISS) for MM stage (Greipp *et al*, 2005), and serum  $\beta_2$ -microglobulin concentration. Cytogenetic/fluorescent *in situ* hybridization (FISH) prognostic markers of high-risk disease were defined per Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART) criteria (Dispenzieri *et al*, 2007) analysed by either FISH [for del17p, t(4;14), or t(14;16)] or by metaphase cytogenetics (for del13 or hypodiploidy). ORR was estimated within each subgroup along with its 95% exact binomial CIs. Analysis for time-to-event secondary endpoints (PFS, TTP, DOR, and OS) was performed by preparing Kaplan-Meier estimates for quartiles including median and Kaplan-Meier curves. Also generated were 2-sided 95% CIs for the quartiles. The event-free rate was estimated for several time points (e.g., 9 months).

Simple descriptive statistics were used to summarize the AE profile of carfilzomib based on the number and percentage of patients experiencing system organ class events. Changes in clinical safety laboratory values and vital signs

were summarized descriptively for each scheduled and unscheduled time point. Changes were calculated relative to the values collected at baseline and on the first day of each treatment cycle.

## Results

### Patient population

A total of 35 bortezomib-treated patients from 17 centres enrolled in this study between September 2007 and November 2008 with a data cutoff of November 2010. All patients received at least one dose of carfilzomib and therefore were evaluable for both safety and efficacy. The median age was 63 years (range 40–77) and the median time from diagnosis was 3.6 years (range 1.2–13.2) (Table I). A high tumour burden was demonstrated by an ISS stage of II or III in 42.9% of patients. A significant proportion of patients had poor/unfavourable markers by cytogenetic or FISH analysis (25.7%), and the median serum  $\beta_2$ -microglobulin concentration at baseline was 3.3 mg/l (range 1.6–9.8). More than half of all patients had active PN at baseline: Grade 1 in 16 patients (45.7%) and Grade 2 in three patients (8.6%). At the time of study entry, a large proportion of patients also had active haematological abnormalities, including anaemia (85.7%), neutropenia (57.1%), and thrombocytopenia (28.6%), all of Grade 1/2 in severity with the exception of one patient with Grade 3 thrombocytopenia.

Patients had received a median of 3.0 prior therapies (range 1–13)(Table II). Five (14.3%) patients received four or more prior regimens, and all patients had been previously treated with bortezomib. More than half of all patients (20; 57.1%) received bortezomib in their treatment regimen immediately preceding study entry. Seven patients (20.0%) were refractory to bortezomib at any time prior to participating in this study, and 22 patients (62.9%) had disease that was refractory to their last therapy regardless of drug. The majority of patients (97.1%) had previously received corticosteroid therapy; other common treatments included alkylating agents (88.6%), thalidomide (68.6%), and lenalidomide (37.1%), and 80.0% of the patients enrolled had undergone autologous stem cell transplant.

### Efficacy

All 35 patients were included in the response-evaluable population, for which the best ORR was 17.1% as determined by an independent central assessment (1 CR, 1 VGPR, and 4 PR), and the CBR rate was 31.4% (Table III). Responses were observed even in those patients with more severe disease at baseline; >10% ORR was reported in subgroups analysed by patient baseline characteristics of ECOG PS and ISS stage prognostic markers, as well as poor/unfavourable markers characterized by cytogenetic analysis (six patients) or FISH analysis (three patients) (Table IV). Although there

**Table I.** Patient baseline characteristics.

Characteristic	Carfilzomib 20 mg/m <sup>2</sup> (N = 35)
Median age, years (range)	63 (40–77)
Male gender	18 (51.4)
Median time from diagnosis, years (range)	3.6 (1.2–13.2)
Immunoglobulin subtype, n (%)	
IgG	24 (68.6)
IgA	5 (14.3)
IgD	1 (2.9)
Unknown/Missing	5 (14.3)
Light chain subtype, n (%)	
Kappa	23 (65.7)
Lambda	12 (34.3)
ECOG PS, n (%)	
0	15 (42.9)
1 or 2	19 (54.3)
ISS Stage, n (%)	
I	19 (54.3)
II	8 (22.9)
III	7 (20.0)
Baseline evaluation, n (%)	
Peripheral neuropathy ≥ Grade 1	19 (54.3)
Diabetes	5 (14.3)
CrCl <50 ml/min	4 (11.4)
β <sub>2</sub> -microglobulin, mg/l (range)	3.3 (1.6–9.8)
Cytogenetic/FISH prognostic markers, n (%)	
Normal/Favourable	25 (71.4)
Unfavourable	9 (25.7)

Ig, immunoglobulin; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; CrCl, creatinine clearance; FISH, fluorescence *in situ* hybridization.

**Table II.** Prior therapies.

	Carfilzomib 20 mg/m <sup>2</sup> (N = 35)
Median number of prior therapies (range)	3.0 (1–13)
Prior therapy, n (%)	
Bortezomib	35 (100.0)
Bortezomib in last regimen	20 (57.1)
Thalidomide	24 (68.6)
Lenalidomide	13 (37.1)
Thalidomide or lenalidomide	27 (77.1)
Corticosteroid	34 (97.1)
Alkylating agent	31 (88.6)
Anthracycline	11 (31.4)
Stem cell transplant	28 (80.0)
Refractory status, n (%)	
To bortezomib in any prior regimen	7 (20.0)
To last therapy,* n (%)	22 (62.9)

\*Most patients received a combination regimen as their last therapy.

were some differences in absolute numbers (e.g., the ORRs between ISS Stages I, II, and III), the small numbers of patients in each subgroup, along with the wide confidence intervals, precluded any firm conclusions to be drawn from differences between or within subgroups. In the response-evaluable subset population (N = 31), in which patients with disease measured by sFLC only were excluded, ORR was 16.1% (1 CR, 1 VGPR and 3 PR) as determined by an independent central assessment.

Responses were fairly rapid, with a median time to response (TTR) of 1.4 months to achieve ≥ PR and

**Table III.** Best overall response (response-evaluable population).

	Carfilzomib 20 mg/m <sup>2</sup> (N = 35)
Best response, n (%)*	
CR	1 (2.9)
VGPR	1 (2.9)
PR	4 (11.4)
MR	5 (14.3)
SD	13 (37.1)
PD	10 (28.6)
ORR (sCR + CR + VGPR + PR)	6 (17.1)
CBR (ORR + MR)	11 (31.4)

CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; ORR, overall response rate; CBR, clinical benefit response.

\*Includes four patients whose disease was followed by sFLC, one of whom had a confirmed response.

**Table IV.** Overall response rate (ORR) of baseline characteristic subgroup.\*

	n	ORR,%	95% CI
Overall	35	17.1	6.6–33.7
Baseline characteristic			
Age group			
<65 years	21	9.5	1.2–30.4
≥ 65 years	14	28.6	8.4–58.1
ECOG PS			
0	15	26.7	7.8–55.1
1 or 2	19	10.5	1.3–33.1
ISS Stage			
I	19	15.8	3.4–39.6
II	8	25.0	3.2–65.1
III	7	14.3	0.4–57.9
Cytogenetic/FISH prognostic markers			
Normal/favourable	25	16.0	4.5–36.1
Poor/unfavourable	9	11.1	0.3–48.2

ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; FISH, fluorescence *in situ* hybridization.

\*Response-evaluable population.

1.0 month to achieve  $\geq$ MR. The median DOR was  $>10.6$  months with four out of the six patients with a DOR of 10.6 months or longer. A more precise estimate of the median DOR could not be determined as four of the six patients with responses had their DOR censored at the close of the study (Table V). Median duration of clinical benefit was 10.6 months and median duration of MR was 7.9 months. The median TTP was 4.6 months (95% CI: 1.9–11.1) (Fig 2) and the median PFS was 4.6 months (95% CI: 2.1–11.1). Median OS was calculated to be 29.9 months; however, survival data remain immature and neither the upper nor lower limit of 95% CI could be estimated as of the data cutoff.

### Safety

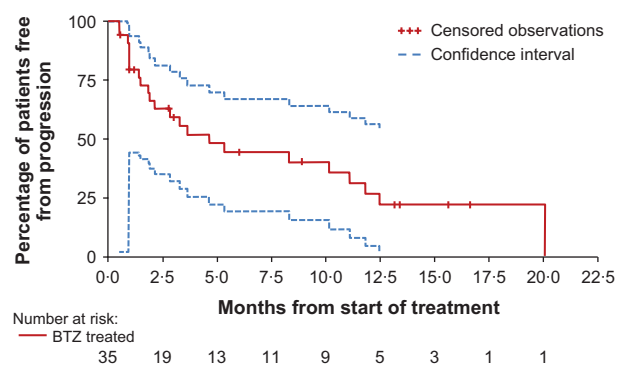
The safety population included all 35 patients enrolled in the study. Patients started a median of four cycles of carfilzomib (range 1–12), and nine patients (25.7%) completed 12 cycles of carfilzomib therapy. Although no patients from this study

**Table V.** Time to progression, time to response, and duration of response.\*

	Carfilzomib 20 mg/m <sup>2</sup> (N = 35)
Median TTP, months (95% CI)	4.6 (1.9–11.1)
Median TTR, months (95% CI)	
$\geq$ PR (ORR)	1.4 (0.5–1.9)
$\geq$ MR (CBR)	1.0 (0.5–6.7)
Median DOR, months (95% CI)	
$\geq$ PR (ORR)	NE (10.6–NE)
$\geq$ MR (CBR)	10.6 (7.2–NE)
MR	7.9 (5.8–14.6)

NE, not estimated due to censoring; TTP, time to progression; TTR, time to response; DOR, duration of response; 95% CI, 95% confidence interval; PR, partial response; MR, minimal response; ORR, overall response rate; CBR, clinical benefit response.

\*Response-evaluable population.



**Fig 2.** Time to Progression. Median time to progression = 4.6 months (95% CI 1.9–11.1).

entered the PX-171-010 extension protocol, 1 patient continued to receive carfilzomib treatment on a single-patient extension protocol for an additional 11 months.

Carfilzomib was generally well tolerated. The most frequent AEs were fatigue (62.9%), nausea (60.0%), vomiting (42.9%), diarrhoea, and dyspnea (both 37.1%) (Table VI). Twenty patients (57.1%) experienced at least one severe (Grade  $\geq$  3) AE, the majority of them (15/20) Grade 3. The most common Grade 3/4 AEs were haematological, including thrombocytopenia (20.0%), anaemia (14.3%), and neutropenia (11.4%). Treatment-related AEs occurred in all patients and the most common were nausea (51.4%), fatigue (48.6%), increased serum creatinine (34.3%), diarrhoea (31.4%), vomiting (31.4%), dyspnea (28.6%), thrombocytopenia (28.6%), and anaemia (25.7%).

Of the 26 patients that discontinued early, 16 patients discontinued due to disease progression and six patients due to treatment-emergent AEs; the only AE leading to discontinuation for more than one patient was hypercalcaemia (two patients). Other reasons for discontinuation were physician

**Table VI.** Safety population treatment-emergent adverse events of all grades ( $\geq$  20%) or  $\geq$  Grade 3 ( $\geq$  5%).

Treatment-emergent adverse event	Carfilzomib 20 mg/m <sup>2</sup> (N = 35)	
	All Grades n (%)	$\geq$ Grade 3 n (%)
<b>Haematological</b>		
Anaemia	12 (34.3)	5 (14.3)
Thrombocytopenia	11 (31.4)	7 (20.0)
Neutropenia	9 (25.7)	4 (11.4)
Lymphopenia	6 (17.1)	2 (5.7)
<b>Non-haematological</b>		
Fatigue	22 (62.9)	1 (2.9)
Nausea	21 (60.0)	1 (2.9)
Vomiting	15 (42.9)	1 (2.9)
Dyspnea	13 (37.1)	2 (5.7)
Diarrhoea	13 (37.1)	0 (0)
Upper respiratory infection	12 (34.3)	2 (5.7)
Increased serum creatinine	12 (34.3)	1 (2.9)
Increased alanine aminotransferase	10 (28.6)	0 (0)
Headache	9 (25.7)	1 (2.9)
Hypoesthesia	9 (25.7)	0 (0)
Pyrexia	9 (25.7)	0 (0)
Asthenia	8 (22.9)	1 (2.9)
Constipation	8 (22.9)	0 (0)
Cough	8 (22.9)	0 (0)
Dizziness	7 (20.0)	0 (0)
Increased aspartate aminotransferase	7 (20.0)	0 (0)
Pain	7 (20.0)	0 (0)
Hypertension	6 (17.1)	2 (5.7)
Hypercalcaemia	5 (14.3)	2 (5.7)
Pneumonia	3 (8.6)	3 (8.6)
Epiglottitis	2 (5.7)	2 (5.7)

discretion and near complete remission (one patient each) as well as patient decision to come off study or withdrew consent (one patient each). No deaths occurred on study (inclusive of 30 d of last carfilzomib dose). Nearly half of the patients (45.7%) received the protocol-specified dosing schedule on time and 62.9% received doses of 90–100% of the relative dose intensity specified in the protocol. Four patients had dose reductions due to AEs, although three of these patients were successfully re-escalated to the 20 mg/m<sup>2</sup> dose.

During the study 6 (17.1%) patients experienced neuropathy-related treatment-emergent AEs; the majority of PN reports were Grade 1 and considered not related to carfilzomib treatment (four patients). Additionally there was one patient with Grade 2 and one patient with Grade 3 (both possibly related to treatment) and no reports of Grade 4 PN. There were no dose reductions or discontinuations due to PN, which is especially notable as 54.3% of all study patients had Grade 1-2 PN at baseline. Moreover, prolonged treatment with carfilzomib as seen in this study was not associated with any significant increase in neuropathy, as supported by the absence of a meaningful change from baseline to the last assessment ( $n = 30$ ) on the FACT/GOG-NTx results.

## Discussion

In this study, the best ORR for the response-evaluable population was 17.1% and the CBR was 31.4%. Additional statistical testing between subgroups was not performed due to the small numbers within subgroups; however, responses of at least 10% were observed even in high-risk patients and those with more severe disease, including poor/unfavourable cytogenetics and ISS stage III based on the subgroup analyses. These results indicate single-agent activity in this population and are interesting because of the very limited data available on retreatment with monotherapies in patients with MM refractory to bortezomib (Mohty *et al*, 2012; van de Donk *et al*, 2011). Because the number of patients in this study was relatively small, caution must be used in interpreting the results. However, the results of this study are comparable to those from previous carfilzomib studies with patients who had similar medical and treatment histories (Alsina *et al*, 2007; Siegel *et al*, 2010).

The majority of carfilzomib doses in this study were administered at the 20 mg/m<sup>2</sup> level. Subsequent studies have demonstrated the tolerability of higher doses including 27 mg/m<sup>2</sup> on the same schedule and 56 mg/m<sup>2</sup> when given as a 30-min infusion (Siegel *et al*, 2010; Papadopoulos *et al*, 2011). Based on the results of other carfilzomib studies with a dosing regimen of 27 mg/m<sup>2</sup>, including the 003-A1 study and the independently analysed bortezomib-naïve cohorts from the 004 study, it is likely that increased anti-MM activity would be observed even at higher dose levels as a single agent (Siegel *et al*, 2010; Vij *et al*, 2010, 2012).

At a median follow-up of 13.4 months (95% CI: 8.9–16.6), the median TTP was 4.6 months (95% CI: 1.9–11.1).

In part, this short median TTP is the result of early disease progression in approximately 50% of patients, most probably due to advanced disease at the time of study entry. For patients remaining on study for more than four cycles, progression events were often substantially delayed, a finding consistent with the promising DOR seen in both patients with  $\geq$ PR and those with  $\geq$ MR. The median DOR of 7.9 months (95% CI: 5.8–14.6) reached for patients experiencing MR suggests that MR may be an equally valid response endpoint and supports the concept that sustained MR is associated with a clinically meaningful benefit (Richardson *et al*, 2005; Niesvizky *et al*, 2008). These results reinforce the suggestion of durable disease control with carfilzomib monotherapy for a significant number of heavily pretreated patients in this study.

Carfilzomib treatment was generally tolerable, with the majority of patients receiving carfilzomib at the planned dose and according to schedule. The fact that patients started a median of four cycles of treatment correlates well with median time to response and indicates that patients are able to tolerate carfilzomib for a long enough interval to see evidence of response. Reinforcing the tolerability profile of carfilzomib from other studies (Siegel *et al*, 2011b; Singhal *et al*, 2011), 25.7% of patients completed a full 12 cycles of treatment and one patient continued on a single-patient extension protocol.

The most common treatment-related AEs were gastrointestinal (nausea, diarrhoea, vomiting, and constipation), constitutional (fatigue), respiratory (dyspnea), and myelosuppressive (thrombocytopenia, anaemia, and neutropenia). When compared with a larger study of carfilzomib with a similar but more heavily treated bortezomib-relapsed and refractory population (PX-171-003) (Siegel *et al*, 2010), the overall AE rates were comparable, although certain toxicities were reported less frequently in this study, namely haematological AEs  $\geq$  Grade 3. Additionally, although an actual comparison cannot be made due to the differences in trial sizes and patient populations, toxicity compared relatively favourably to bortezomib—in the Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial comparing treatment of bortezomib and dexamethasone in patients with relapsed MM, 9% of patients completed the planned bortezomib therapy compared with the 25.7% here, and 37% had AEs resulting in discontinuation of bortezomib compared with the 17.1% that discontinued due to an AE here (Richardson *et al*, 2005).

PN is a common occurrence in patients with MM and is both caused and exacerbated by treatment with bortezomib and thalidomide. PN has been reported in up to 70% of patients treated with thalidomide and approximately 37% of patients treated with bortezomib (Mohty *et al*, 2010). Therefore, the occurrence of PN was carefully monitored in this study. The incidence of neuropathy at baseline for this study was >50%, but exacerbations were not observed upon carfilzomib treatment. Similarly, previous studies have found that baseline PN does not impact the efficacy and tolerability of carfilzomib (Martin *et al*, 2010). Additionally, patients'

self-reported experiences and quality of life in the current study were minimally impacted from the initiation of the study through to their last assessment, further supporting the PN-specific tolerability of this agent.

In summary, single-agent carfilzomib at 20 mg/m<sup>2</sup> achieved significant responses in this heavily pre-treated population, including treatment with bortezomib and the immunomodulatory agents thalidomide and lenalidomide. Treatment with carfilzomib was well tolerated for up to 12 cycles, and a lack of significant toxicities supports the use of single-agent carfilzomib or potential combination regimens. The results of the larger phase 2 study of carfilzomib therapy in heavily pretreated patients with relapsed and refractory MM, including a significant proportion of patients previously treated with bortezomib (PX-171-003-A1, NCT00511238), further demonstrate the efficacy of carfilzomib in this population (Siegel *et al*, 2010, 2011c). Ongoing studies are investigating the use of carfilzomib in combination with other agents and its use in patients with newly diagnosed MM.

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## Authors' contributions

RV designed the research, performed research, contributed vital new reagents or analytical tools, and analysed data. DSS designed research, performed research and analysed data. SJ designed research, performed research and analysed data. AJJ

performed research and analysed data. AKS designed research, performed research and analysed data. KM performed research. NB performed research. AB performed research. LAK designed research, contributed vital new reagents or analytical tools, and analysed data. SW performed research and analysed data. AFW designed research, contributed vital new reagents or analytical tools, and analysed data. RZO designed the research, performed research, and analyzed data. MW performed research and analysed data. The investigators and representatives from Onyx Pharmaceuticals Inc. designed the study. The data were collected and analysed by medical and statistical representatives from Onyx Pharmaceuticals Inc. in conjunction with the investigators. All authors had access to the primary data and participated in writing and editing this paper. All participating institutions received support from Onyx Pharmaceuticals Inc. for the conduct of the study.

## Conflicts of Interest

The authors declare the following: RV: consultancy and research funding for Onyx Pharmaceuticals Inc. DSS: consultancy, honoraria, and board of directors or advisory committee membership for Millennium and Celgene. SJ: honoraria for Millennium, Celgene, Onyx Pharmaceuticals Inc., and Merck; board of directors or advisory committee membership for Ortho Biotech, Imedex, Medicom Worldwide, Optum Health Education, and PER Group. AJJ: consultancy for Ortho Biotech, Celgene, Millennium, Onyx Pharmaceuticals Inc., Bristol-Myers Squibb, and Exelixis; honoraria for Ortho Biotech, Celgene, Millennium, Bristol-Myers Squibb, and Exelixis; speakers bureau for Ortho Biotech, Celgene, and Millennium; board of directors membership for Millennium, Onyx Pharmaceuticals Inc., and Bristol-Myers Squibb; advisory committee membership for Onyx Pharmaceuticals Inc. and Bristol-Myers Squibb. AKS: consultancy and research funding for Celgene, Millennium, Novartis, Bristol-Myers Squibb, and Onyx Pharmaceuticals Inc. KM: No relevant financial relationship(s) to disclose. NB: honoraria and speakers bureau for Celgene. AB: No relevant financial relationship(s) to disclose. LAK: consultancy for VLST Biotech, Threshold, and Onyx Pharmaceuticals Inc. SW: No relevant financial relationship(s) to disclose. AFW: employed by and equity ownership in Onyx Pharmaceuticals Inc. RZO: Honoraria and Board of Directors or advisory committee membership for Onyx Pharmaceuticals. MW: research funding for Onyx Pharmaceuticals Inc.

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