

# A phase 1/2 study of carfilzomib in Japanese patients with relapsed and/or refractory multiple myeloma

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## Summary

We conducted a phase 1/2 study of single-agent carfilzomib in Japanese patients with relapsed/refractory multiple myeloma. Safety, pharmacokinetics and pharmacodynamics of carfilzomib were examined in phase 1. The primary endpoint in phase 2 was the overall response rate (ORR). Carfilzomib was administered in a twice-weekly, consecutive-day dosing schedule. In Phase 1, doses of 15 or 20 mg/m<sup>2</sup> were administered on this schedule or 20 mg/m<sup>2</sup> on Days 1 and 2 of Cycle 1 and then 27 mg/m<sup>2</sup> in the 20/27 mg/m<sup>2</sup> cohort. Patients had a median of five prior therapies, including bortezomib and an immunomodulatory agent. The dose level did not reach the maximum tolerated dose. The most common adverse events were haematological. Notably, carfilzomib either induced new hypertension ( $n = 4$ ) or aggravated previously existing hypertension ( $n = 6$ ) in 10 of 50 patients. Four of the eight patients who previously experienced peripheral neuropathy (PN) experienced a recurrence with carfilzomib use, but no new cases of PN occurred. The ORR of the 20/27 mg/m<sup>2</sup> 40 patient cohort was similar to that in the pivotal US study. The dose was efficacious and tolerable in heavily pre-treated Japanese patients; however, meticulous control of hypertension may be necessary for further carfilzomib use.

**Keywords:** multiple myeloma, carfilzomib, hypertension peripheral neuropathy, cardiovascular AEs.

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Multiple myeloma (MM) is characterized by the abnormal accumulation of clonal plasma cells in the bone marrow. In the United States (US), an estimated 21 700 new cases of MM and 10710 deaths were predicted in 2012 (American Cancer Society 2012); in Japan, an estimated 6860 new cases of MM and 4066 deaths ([http://ganjoho.jp/reg\\_stat/statistics/dl/](http://ganjoho.jp/reg_stat/statistics/dl/)) were predicted. Over the past decade, the introduction of immunomodulators, such as thalidomide and lenalidomide, and a proteasome inhibitor (PI) bortezomib (Velcade<sup>®</sup>, Millennium Pharmaceuticals, Cambridge, MA, USA) has significantly improved the overall survival (OS) of MM patients (Jemal *et al*, 2010).

Carfilzomib (Kyprolis<sup>®</sup>, Onyx Pharmaceuticals, an Amgen subsidiary, South San Francisco, CA, USA) is one of the second-generation epoxyketone PIs that can irreversibly inhibit chymotrypsin-like activity (Demo *et al*, 2007; Parlati *et al*, 2009). Carfilzomib induced apoptosis in myeloma cell lines and primary myeloma cells from patients whose disease was resistant to available therapies, including bortezomib (Kuhn *et al*, 2007). In addition, carfilzomib has fewer off-target effects, which may explain a lack of neurodegeneration *in vitro*, and less neurotoxicity in animal studies (Arastu-Kapur *et al*, 2011). Therefore, carfilzomib was expected to circumvent some of the clinical adverse events (AEs) of bortezomib, particularly peripheral neuropathy (PN) (Bruna *et al*, 2010; Arastu-Kapur *et al*, 2011).

In fact, PN did not appear to be clinically limiting for extended carfilzomib treatment (Vij *et al*, 2012a,b). An alternative subcutaneous route of administration for bortezomib reduced the incidence of PN without reducing efficacy (Moreau *et al*, 2011). Despite these facts, the subcutaneous administration of bortezomib has still caused gastrointestinal (GI) AEs in patients with MM (Moreau *et al*, 2011). Carfilzomib has also caused GI AEs; however, those occurring with carfilzomib use were mild and manageable with routine supportive care (Siegel *et al*, 2012; Vij *et al*, 2012b).

Almost all patients with MM will eventually relapse, and new treatment options are needed. Accordingly, to change the intrinsic natural behaviour of MM, it was suggested that the use of higher doses, combination regimens and early treatment of the disease course without AEs are required for the new treatment using carfilzomib (Reece, 2012). However,

discontinuation or dose reduction was inevitable because of increased toxicities in some of the carfilzomib trials using combination therapies (Bringhen *et al*, 2014; Sonneveld *et al*, 2015).

In an open-label, phase 2 pilot study (PX-171-003-A0) of carfilzomib in 46 patients with relapsed/refractory MM (RRMM), patients treated with carfilzomib 20 mg/m<sup>2</sup> achieved an overall response rate (ORR) of 16.7%, with manageable toxicities (Jaganath *et al*, 2012). The study was subsequently amended to include an expanded dosing cohort with a scheduled dose escalation from 20 to 27 mg/m<sup>2</sup> beginning in the second cycle (PX-171-003-A1 [003-A1]). In 003-A1, which included 266 patients with RRMM, the ORR was 23.7%; these results were the basis for the accelerated approval of carfilzomib by the US Food and Drug Administration (Siegel *et al*, 2012). In the present study, we used the same dose escalation schedule as 003-A1, with one exception: 27 mg/m<sup>2</sup> was started on Day 8 of Cycle 1. With this method, we carefully characterized the AEs of carfilzomib in a phase 1/2 single-agent carfilzomib study in Japanese patients with RRMM.

## Methods

### Study design

This was a multicentre, open-label phase 1/2 study (ONO-7057-01) in Japanese patients with RRMM. The safety, tolerability, efficacy, pharmacokinetics (PK) and pharmacodynamics of carfilzomib were examined in phase 1 for intravenously administered carfilzomib at doses of 15, 20 and 20/27 mg/m<sup>2</sup>. Phase 2 examined the safety and efficacy of carfilzomib at the recommended dose determined in phase 1. The primary endpoint in phase 2 was the ORR. Secondary endpoints included the duration of response (DOR), Progression-free survival (PFS) and OS. It was planned that three or six patients for each cohort in phase 1 and 24 patients in phase 2 were enrolled. If dose-limiting toxicity (DLT) occurred in one of three patients, an additional three patients were enrolled; if the incidence of DLT was two of three patients or three of six patients, the previous dose level was used as the recommended dose in phase 2.

### Eligibility

The main patient inclusion criteria were age  $\geq 20$  years and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. Patients were required to have relapsed myeloma and measurable disease (either serum M protein level of  $\geq 5.0$  g/l or urinary M protein of  $\geq 0.2$  g/24 h) responsive to at least one previous therapeutic regimen ( $\geq 25\%$  of reduction in M or total protein) and refractory to their most recent therapy (disease progression either during treatment or within 60 days after therapy completion). Patients were to be exposed to at least three prior treatments, including bortezomib, an immunomodulatory agent (lenalidomide and/or thalidomide), an alkylating agent, a corticosteroid and anthracycline (except for patients ineligible or clinically unsuitable for transplantation). Patients were excluded if they had Grade  $\geq 3$  or Grade 2 PN with pain or a past history of interstitial lung disease (ILD), congestive heart failure (CHF) of New York Heart Association class  $\geq III$ , symptomatic myocardial ischaemia or uncontrolled conduction abnormalities.

This study was conducted in compliance with the Good Clinical Practice guidelines. The study protocol was approved by the Institutional Review Board of each institution, and written informed consent was obtained from each patient enrolled in this study.

### Dose-limiting toxicity definition

DLT was defined as any of the following AEs in Cycle 1 that were at least possibly related to carfilzomib and met one of the following criteria: Grade 3 or 4 PN or Grade 2 PN with pain; Grade  $\geq 3$  non-haematological toxicities; Grade  $\geq 3$  nausea, vomiting or diarrhoea that was uncontrolled after an adequate administration of anti-emetic or anti-diarrhoeal medications; febrile neutropenia; Grade 4 neutropenia persisting for  $>8$  days without using granulocyte-colony stimulating factor (G-CSF) for supportive therapy and Grade 4 thrombocytopenia that required platelet transfusion or was accompanied by bleeding. Administration of G-CSF was not permitted during the DLT evaluation period.

### Treatment

Carfilzomib was intravenously administered for 10 min at doses of 15, 20 and 20/27 mg/m<sup>2</sup> on Days 1, 2, 8, 9, 15 and 16 of each 28-day cycle until withdrawal of consent, disease progression or the occurrence of unacceptable toxic effects. For the 20/27 mg/m<sup>2</sup> dosage, 20 mg/m<sup>2</sup> was dosed on Days 1 and 2 of Cycle 1 and escalated to 27 mg/m<sup>2</sup> on Day 8 of Cycle 1 and thereafter.

Oral or intravenous dexamethasone (4 mg) was administered before each dose of carfilzomib in Cycle 1 and thereafter if necessary as pre-medication to prevent infusion reactions. Intravenous and oral hydrations were also required

during Cycle 1 and in subsequent cycles as needed. In Cycle 1, all patients were required to receive prophylactic antibiotics, and patients with a medical history of herpes infection received acyclovir.

### Assessment of response and safety

The efficacy analysis set comprised all patients who received at least one dose of carfilzomib and had at least one assessment of efficacy or pharmacodynamics. The primary endpoint of phase 2 was the ORR based on central laboratory data according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Durie *et al*, 2006), including the minimal response (MR), as defined by the European Group for Blood and Marrow Transplantation criteria (Bladé *et al*, 1998). The ORR with 95% confidence interval (CI) was determined for each dose level. The investigational period ended when Cycle 6 was completed for all patients enrolled in the study, and subsequent cycles were included in the analysis for patients whose therapy lasted more than six cycles.

The safety analysis set comprised all patients who received at least one dose of carfilzomib, and all AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 ([http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4-03\\_2010-06-14\\_Quick-Reference\\_8-5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4-03_2010-06-14_Quick-Reference_8-5x11.pdf)).

### Pharmacokinetics and pharmacodynamics

Samples for determining the plasma concentrations of carfilzomib were collected on Days 1 and 16 of Cycle 1 before administration, 5 min after the start of administration, immediately before the completion of administration and 5, 15 and 30 min and 1, 2 and 4 h after administration was completed. Moreover, whole blood and peripheral blood mononuclear cells (PBMCs) were collected on Days 1, 2 and 8 of Cycle 1 and Day 1 of Cycle 2 before administration as well as at 1 h after administration was completed to analyse proteasome activity.

### Statistical analyses

All statistical analyses were performed using SAS<sup>®</sup> version 9.3 (SAS Institute Inc., Cary, NC, USA). Two-sided 95% CI of the best ORR was determined according to Willson (1927) for evaluable patients whose best response was classified as stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR).

The analysis of the ORR was performed in subgroups, defined by the patient baseline characteristics of age, sex, cytogenetics/fluorescence *in situ* hybridization (FISH) and International Staging System (ISS) for MM stage (Greipp *et al*, 2005) as exploratory analyses. Patients were classified as

having standard-risk or high-risk cytogenetic abnormalities, as defined by IMWG criteria (Munshi *et al*, 2011). High-risk cytogenetic markers included either del 13 or hypodiploidy by metaphase cytogenetic analysis and/or del 17p13, t(4;14), t(14;16) by interphase FISH. Hence, patients without these abnormalities were considered to be standard risk.

The ORR was estimated within each subgroup along with its 95% Wilson CI. The clinical benefit rate (CBR) is the percentage of patients whose best response was classified as CR, VGPR, PR and MR. The CBR was estimated along with its 95% Wilson CI. Analysis for time-to-event (PFS and OS) was performed by preparing Kaplan–Meier estimates of the median and plotting Kaplan–Meier curves. In addition, two-sided 95% CIs for the medians were estimated.

## Results

### *Patients and characteristics*

Fifty patients were enrolled from 15 centres in Japan between August 2011 and January 2014; patient characteristics are shown in Table I. The median age was 67 years (range, 48–81 years), and the median time from initial diagnosis to study entry was 4.7 years (range 1.6–12.6 years). Most patients had either immunoglobulin G- (70%) or immunoglobulin A-type (16%) myeloma, and 58% had ISS stage II or III at diagnosis. A significant proportion of patients (32%) had poor/unfavourable karyotypes, as determined by FISH analysis. The majority of patients (70%) had Grade 1 or 2 PN at baseline, and 40 of the 50 enrolled patients had past medical history of PN.

The patients had previously received a median of five (range 3–10) therapies, and 42% had previously received at least six therapies. All patients had received bortezomib and an immunomodulatory agent in previous regimens, and 48% had received at least two lines of bortezomib-containing regimens. Twenty (40%) patients had undergone autologous stem cell transplantation (ASCT) (Table I).

### *Dose escalation*

Seventeen of the 50 patients enrolled in the study were enrolled in phase 1. Four patients, including one patient who was not evaluable for DLT, were enrolled in the 15 mg/m<sup>2</sup> cohort; no DLT was observed.

One of the first three patients experienced DLT (thrombotic microangiopathy, cardiomyopathy, hepatic disorder and sensorimotor disorder) in the 20 mg/m<sup>2</sup> cohort; therefore, an additional three patients were enrolled at this level. No further DLT was observed in the three patients; subsequently, no DLT was observed in a total of seven patients (including one who was not evaluable for DLT) enrolled in the 20/27 mg/m<sup>2</sup> cohort, thereby suggesting that a higher dose could reasonably be tested. However, 20/27 mg/m<sup>2</sup> was determined to be the recommended dose in phase 2 of this

Japanese study at that time, considering the results in the previous carfilzomib studies conducted overseas (Siegel *et al*, 2012).

### *Efficacy*

Fifty patients were included in the efficacy analysis set; the ORR was 20.0% and the CBR was 28.0% (Table II). In the 40 patients who received the 20/27 mg/m<sup>2</sup> dose, the ORR was 22.5% and the CBR was 27.5%. Subgroup analysis of the 20/27 mg/m<sup>2</sup> group demonstrated that the ORR was not affected by age and ISS stage (Table III). The comparison of the 20/27 mg/m<sup>2</sup> group in this study with that in the 003-A1 study (Siegel *et al*, 2012) showed that the results were similar (22.5% vs. 23.7%) (Table III). In the 20/27 mg/m<sup>2</sup> group, the median DOR was not reached (95% CI, 2.3 months–not reached), and the median PFS was 5.1 months (95% CI: 2.8–7.0 months), whereas the median OS was not reached (95% CI: 7.4 months–not reached) at the time of the data cut-off. The median follow-up times for PFS and OS were 6.0 months (95% CI: 5.8–6.7 months) and 6.5 months [95% CI: 6.0–7.2 months], respectively.

### *Safety*

Fifty patients who received at least one dose of carfilzomib were included in the safety population. All patients experienced at least one AE, and 88% had at least one AE of Grade  $\geq 3$ . All AEs encountered in  $\geq 20\%$  of the patients are shown in Table SI. The most commonly observed AEs were haematological toxicities, including lymphopenia (86%), thrombocytopenia (68%), anaemia (58%), neutropenia (56%) and leucopenia (50%). The most commonly observed AEs of Grade  $\geq 3$  were lymphopenia (68%), neutropenia (38%), anaemia (30%), thrombocytopenia (26%) and leucopenia (26%).

Although PN was observed in eight patients (16%), none were of Grade  $\geq 3$ , and four of the eight patients had PN of Grade 1 or 2 at the baseline of the study. Moreover, all eight patients had a past history of PN before enrolment in the study (Table IV). According to the detailed analysis of the history of PN, 45 (90%) of 50 patients had experienced PN before they were enrolled in the study; however, PN in 10 of the 45 patients resolved before enrolment. Subsequently, four of the 10 patients encountered PN again after carfilzomib treatment (Patients 2, 3, 5 and 7 in Table IV). In total, eight (18%) of the 45 patients developed PN again after carfilzomib treatment and, of the 35 patients who had PN at baseline (Table I), carfilzomib exacerbated PN in three patients (6% of 50 enrolled patients, 8.6% of the 35 patients) (Patients 1, 4 and 6 in Table IV). In contrast, the remaining five patients who had never experienced PN before enrolment into the carfilzomib study did not develop PN after carfilzomib treatment. One patient who had Grade 2 PN of the lower extremities at baseline newly developed a trigeminal nerve

Table I. Patients' baseline characteristics.

Characteristic	15 mg/m <sup>2</sup> (n = 4)		20 mg/m <sup>2</sup> (n = 6)		20/27 mg/m <sup>2</sup> (n = 40)		Total (N = 50)	
Sex, n (%)								
Male	3	(75)	5	(83)	18	(45)	26	(52)
Median age, years (range)	67	(57–80)	71	(59–80)	66	(48–81)	67	(48–81)
ECOG PS, n (%)								
0	3	(75)	3	(50)	23	(58)	29	(58)
1	1	(25)	3	(50)	17	(43)	21	(42)
ISS stage*, n (%)								
I	2	(50)	2	(33)	12	(30)	16	(32)
II	1	(25)	3	(50)	14	(35)	18	(36)
III	1	(25)	1	(17)	9	(23)	11	(22)
Unknown	0	(0)	0	(0)	5	(13)	5	(10)
Ig subtype, n (%)								
IgG	3	(75)	1	(17)	31	(78)	35	(70)
IgA	1	(25)	5	(83)	2	(5)	8	(16)
IgD	0	(0)	0	(0)	2	(5)	2	(4)
Bence-Jones	0	(0)	0	(0)	5	(13)	5	(10)
Cytogenetic/FISH prognostic markers, n (%)								
Normal/Favourable	1	(25)	5	(83)	25	(63)	31	(62)
Unfavourable†	3	(75)	1	(17)	12	(30)	16	(32)
Unknown	0	(0)	0	(0)	3	(8)	3	(6)
Peripheral neuropathy, n (%)								
Grade 0	0	(0)	1	(17)	14	(35)	15	(30)
Grade 1	2	(50)	4	(67)	20	(50)	26	(52)
Grade 2	2	(50)	1	(17)	6	(15)	9	(18)
Previous lines of therapy, median (range)	5	(4–7)	6	(3–8)	5	(3–10)	5	(3–10)
≥6, n (%)	2	(50)	3	(50)	16	(40)	21	(42)
Baseline anti-hypertensive therapy, n (%)								
Yes	3	(75)	1	(17)	14	(35)	18	(36)
No	1	(25)	5	(83)	26	(65)	32	(64)
Previous therapy, n (%)								
Bortezomib	4	(100)	6	(100)	40	(100)	50	(100)
Immunomodulatory agent								
Lenalidomide	4	(100)	6	(100)	33	(83)	43	(86)
Thalidomide	2	(50)	4	(67)	23	(58)	29	(58)
Corticosteroid	4	(100)	6	(100)	40	(100)	50	(100)
Alkylating agent	4	(100)	6	(100)	40	(100)	50	(100)
Anthracycline	2	(50)	4	(67)	26	(65)	32	(64)
Stem cell transplantation	1	(25)	2	(33)	17	(43)	20	(40)

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

\*At diagnosis.

†Includes either t(4;14), t(14;16) or del (17p).

disorder of Grade 1 during carfilzomib treatment, whereas the pre-existing PN was not aggravated by carfilzomib (Table IV). No ILD was observed.

We particularly highlighted cardiovascular and infectious AEs in this study, and the details are presented in Table V. In total, the occurrence rate of hypertension (HT) was low and similar to that reported in the previous study (17%) (Grade ≥3; 6%) (Vij *et al*, 2012a). In the present study, HT (10/50 patients; 20%) was relatively common among the cardiovascular AEs. Although HT (8%) of Grade ≥3 and

cardiomyopathy (2%) of Grade ≥3 were observed, severe CHF was not reported. The AEs considered to be autonomic are also shown in Table SII, although they were mild, except HT. Among AEs of any grade, HT was the most commonly noted; moreover, as observed in four patients, HT was the only Grade ≥3 AE that was attributed to autonomic neuropathy.

With respect to infectious AEs, it is notable that nasopharyngitis and pharyngitis were relatively common, but the incidence of other infectious AEs was low, a finding



Table II. Best overall response.

	15 mg/m <sup>2</sup> (n = 4)		20 mg/m <sup>2</sup> (n = 6)		20/27 mg/m <sup>2</sup> (n = 40)		Total (N = 50)	
Best response, n (%)								
CR	0	(0)	0	(0)	0	(0)	0	(0)
VGPR	0	(0)	0	(0)	2	(5.0)	2	(4.0)
PR	1	(25.0)	0	(0)	7	(17.5)	8	(16.0)
MR	0	(0)	2	(33.3)	2	(5.0)	4	(8.0)
SD	1	(25.0)	1	(16.7)	16	(40.0)	18	(36.0)
PD	0	(0)	1	(16.7)	9	(22.5)	10	(20.0)
NE	2	(50.0)	2	(33.3)	4	(10.0)	8	(16.0)
ORR (≥PR), n (%)	1	(25.0)	0	(0)	9	(22.5)	10	(20.0)
CBR (≥MR), n (%)	1	(25.0)	2	(33.3)	11	(27.5)	14	(28.0)
DOR, median (95% CI), months	9.5	(NR–NR)	–	–	NR	(2.3–NR)	9.5	(2.3–9.5)
PFS, median (95% CI), months	2.8	(1.7–15.9)	11.1	(0.9–11.1)	5.1	(2.8–7.0)	5.1	(2.8–7.0)
OS, median (95% CI), months	17.9	(3.0–NR)	17.8	(3.4–23.4)	NR	(7.4–NR)	23.4	(10.3–NR)

CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate; CBR, clinical benefit rate; DOR, duration of response; NR, not reached; PFS, progression-free survival; CI, confidence interval; OS, overall survival; NR, not reached.

Table III. Comparison of overall response rate in the 20/27 mg/m<sup>2</sup> cohort according to baseline characteristics.

Characteristic	ONO-7057-01*			PX-171-003-A1†			Odds ratio	95% CI	P-value‡
	n	ORR	95% CI	n	ORR	95% CI			
Overall	40	22.5	12.3–37.5	257	23.7	18.7–29.4	0.93	0.42–2.07	0.8640
Age									
<65 years	12	25.0	8.9–53.2	139	25.2	18.2–33.2	0.99	0.25–3.87	0.9890
≥65 years	28	21.4	10.2–39.5	118	22.0	14.9–30.6	0.97	0.35–2.63	0.9445
Sex									
Female	22	13.6	4.7–33.3	108	29.6	21.2–39.2	0.38	0.10–1.36	0.1232
Male	18	33.3	16.3–56.3	149	19.5	13.4–26.7	2.07	0.72–5.98	0.1720
Cytogenetics/FISH prognostic markers									
Normal/Favourable	25	28.0	14.3–47.6	158	22.8	16.5–30.1	1.32	0.51–3.40	0.5677
Unfavourable	12	16.7	4.7–44.8	71	29.6	19.3–41.6	0.48	0.10–2.36	0.3554
ISS stage									
I	12	25.0	8.9–53.2	76	31.6	21.4–43.3	0.72	0.18–2.91	0.6461
II	14	7.1	1.3–31.5	96	24.0	15.8–33.7	0.24	0.03–1.97	0.1547
III	9	33.3	12.1–64.6	78	17.9	10.2–28.3	2.29	0.51–10.26	0.2704

ORR, overall response rate; CI, confidence interval; FISH, fluorescence *in situ* hybridization; ISS, International Staging System.

\*Present study. For the 20/27 mg/m<sup>2</sup> cohort, 20 mg/m<sup>2</sup> was dosed on Days 1 and 2 of Cycle 1 and escalated to 27 mg/m<sup>2</sup> on Day 8 of Cycle 1 and thereafter.

†Siegel *et al* (2012). The dose for Cycle 1 was 20 mg/m<sup>2</sup>, which was escalated to 27 mg/m<sup>2</sup> on Day 1 of Cycle 2 and thereafter.

‡ $\chi^2$  test.

similar to those for the upper respiratory tract documented previously in patients treated with bortezomib (Shah *et al*, 2004; Teh *et al*, 2014a,b) and carfilzomib (31–34%) (Vij *et al*, 2012a,b). Regarding AEs of Grade ≥3, pneumonia, bronchopneumonia, viral pneumonia, staphylococcal infection and herpes virus infection were observed in one patient each in the study (Table V).

No AEs led to death during the administration period of carfilzomib or within 30 days after the final administration

of carfilzomib. Eight patients (16%) discontinued treatment, and dosing was interrupted or reduced in 24 patients (48%) because of AEs. It is noteworthy that infection was the most frequent reason for the interruption of carfilzomib treatment. Of the 24 patients whose treatment was interrupted, 11 (46%) experienced viral or upper respiratory diseases, including one patient with flu, one with viral disease, eight with upper respiratory diseases and one with fever who was given an anti-inflammatory drug commonly used

**Table IV.** Patients with peripheral neuropathy under study treatment.

Patient No.	Dose level (mg/m <sup>2</sup> )	Preferred terminology (Grade)	Baseline PN Grade	Worst PN Grade before the study
1	20	Peripheral neuropathy (2)	1	3
2	20/27	Peripheral neuropathy (1)	0	2
3	20/27	Peripheral sensory neuropathy (1)	0	2
4	20/27	Peripheral sensory neuropathy (2)	1	3
5	20/27	Peripheral sensory neuropathy (1)	0	2
6	20/27	Peripheral sensory neuropathy (2)	1	3
7	20/27	Peripheral sensory neuropathy (1)	0	1
8*	20/27	Trigeminal nerve disorder (1)	2	2

PN, peripheral neuropathy.

\*Developed trigeminal nerve disorder during carfilzomib treatment. Patient had Grade 2 PN of the lower extremities at baseline, which was not aggravated by carfilzomib.

**Table V.** Adverse events related to cardiovascular disorders and infections of all grades or  $\geq$ Grade 3.

Dose (mg/m <sup>2</sup> )	15 mg/m <sup>2</sup>		20 mg/m <sup>2</sup>		20/27 mg/m <sup>2</sup>		Total	
	(n = 4)		(n = 6)		(n = 40)		(N = 50)	
Patients	All Grades	$\geq$ Grade 3	All Grades	$\geq$ Grade 3	All Grades	$\geq$ Grade 3	All Grades	$\geq$ Grade 3
<b>Cardiovascular disorder</b>								
Hypertension	2	0	2	0	6	4	10	4
Congestive Heart failure	0	0	0	0	2	0	2	0
Vascular pain	0	0	0	0	2	0	2	0
Hot flush	0	0	0	0	2	0	2	0
Atrioventricular block first degree	0	0	0	0	1	0	1	0
Palpitations	0	0	0	0	1	0	1	0
Dyspnoea*	0	0	0	0	1	0	1	0
Vasculitis	0	0	0	0	1	0	1	0
Troponin T increased	0	0	0	0	1	0	1	0
Orthostatic hypotension	1	0	0	0	0	0	1	0
Cardiomyopathy	0	0	1	1	0	0	1	1
<b>Infections</b>								
Nasopharyngitis	0	0	1	0	10	0	11	0
Pharyngitis	1	0	0	0	5	0	6	0
Gingivitis	1	0	0	0	1	0	2	0
Pneumonia	0	0	1	1	1	0	2	1
Bronchopneumonia	0	0	0	0	1	1	1	1
Influenza	0	0	0	0	1	0	1	0
Viral pneumonia	0	0	0	0	1	1	1	1
Upper respiratory tract infection	0	0	0	0	1	0	1	0
Enteritis infection	0	0	0	0	1	0	1	0
Lip infection	0	0	0	0	1	0	1	0
Oropharyngeal candidiasis	0	0	1	0	0	0	1	0
Staphylococcal infection	0	0	1	1	0	0	1	1
Herpes virus infection	0	0	1	1	0	0	1	1

\*Dyspnoea is classified as a respiratory adverse event according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 ([http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)).

as a medicine for cold. In addition, three patients were believed to have infections leading to treatment interruption; these three patients included one patient with pneumonia and two with fever (of three events), for which levofloxacin or acetaminophen was prescribed. The treatment was interrupted in five other patients who developed neutropenia (of seven events).

Our findings indicate that carfilzomib 20/27 mg/m<sup>2</sup> is feasible for Japanese patients with RRMM.

#### *Pharmacokinetics and pharmacodynamics*

PK analyses were performed in a total of 17 patients in phase 1. The PK parameters for carfilzomib are shown in

Table SIII. The plasma carfilzomib concentration showed a rapid decrease after intravenous administration with terminal half-lives ( $T_{1/2}$ ) of 0.424–0.706 h. In the dose range of 15–27 mg/m<sup>2</sup>, the area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration ( $AUC_{last}$ ) and maximum plasma concentration ( $C_{max}$ ) increased in a dose-dependent manner. There was no trend toward increasing or decreasing the clearance and volume of distribution at steady state over the dose range. Following repeated doses of carfilzomib at 15 and 20 mg/m<sup>2</sup>, the PK parameters were similar on Days 1 and 16. Although  $C_{max}$  was measured, the results were not compared with those of previous studies because the duration of intravenous administration of carfilzomib was 10 min in the present study and 2–10 min in the overseas studies (PX-171-007; Papadopoulos *et al*, 2013). Therefore, we concluded that there was no remarkable ethnic difference in the PK parameters of carfilzomib compared with the  $AUC_{last}$  and  $T_{1/2}$  in PX-171-007.

For all dosing levels of carfilzomib, the proteasome activities in whole blood and PBMCs were reduced 1 h after administration on Days 1, 2 and 8 of Cycle 1 and on Day 1 of Cycle 2 with  $\geq 80\%$  inhibition. Furthermore, although proteasome activity in whole blood before the administration of carfilzomib on Day 1 of Cycle 2 slightly recovered ( $\geq 70\%$  inhibition) because drug interruption was longer during this period than during other parts of the administration period, administration of carfilzomib resulted in a similar level of inhibition of proteasome activity. The level of inhibition was  $\geq 80\%$ , which was similar to that obtained in the overseas studies (Alsina *et al*, 2012).

## Discussion

The present study aimed to evaluate the efficacy and safety of single-agent carfilzomib in Japanese patients with RRMM. The dose level did not reach the MTD, but the recommended dose in phase 2 was determined to be 20/27 mg/m<sup>2</sup> on the basis of the results of phase 1. The results of single-agent carfilzomib at a 20/27 mg/m<sup>2</sup> dose showed good responses in heavily pre-treated patients, with an ORR of 22.5% and a median PFS of 5.1 months.

A comparison of the 20/27 mg/m<sup>2</sup> group in this study with that in the pivotal US study (003-A1) (Siegel *et al*, 2012) showed that the results of the ORR were similar (22.5% and 23.7%, respectively), the median number of previous lines of therapy of the 20/27 mg/m<sup>2</sup> group of each study were the same and the proportion of patients with poor prognosis according to cytogenetic abnormalities was 30% in this study (Table I) and 28% in 003-A1. However, the median PFS was better in this study than in 003-A1 (5.1 months vs. 3.7 months, respectively). The following factors account for the difference: 1) no patients with ECOG PS 2 were enrolled in this study, whereas 13% of the enrolled patients in 003-A1 were PS 2, and 2) the median cumulative carfilzomib dose in this study was 796 mg/m<sup>2</sup> (range

80–1363 mg/m<sup>2</sup>), which was much higher than the 470 mg/m<sup>2</sup> (range 20–2647 mg/m<sup>2</sup>) in 003-A1. On the other hand, ethnic differences in the efficacy of carfilzomib did not seem to be significant, and both studies demonstrated good efficacy in patients with RRMM.

The incidences of PN were similar: PN of any grade occurred in 73/526 (13.9%) patients; Grade  $\geq 3$  PN occurred in seven (1.3%) patients in the integrated analysis of four phase 2 studies of single-agent carfilzomib (Siegel *et al*, 2013), whereas PN of any grade was encountered in eight (16.0%) patients and no patient developed PN of Grade  $\geq 3$  in the present study. In addition, of the 35 patients who had PN at baseline, carfilzomib aggravated PN in three patients (8.6%), which contrasts with the results of a previous study (Vij *et al*, 2012b). However, none of the patients who had not previously experienced PN developed new PN. There may be some patients who are prone to develop PN induced by PIs (Broyl *et al*, 2010; Corthals *et al*, 2011; Watanabe *et al*, 2013), and the choice of carfilzomib among PIs decreases the chance of encountering PN that hinders patients with MM from continuing to receive currently efficacious treatment or future treatment for RRMM.

Adverse effects of particular interest have been cardiac events, previously reported for single-agent carfilzomib treatment (Siegel *et al*, 2012; 2013). Aggregated cardiac AEs, including arrhythmia, CHF, ischaemic heart disease and cardiomyopathy, have been reported in 116 of 526 patients (22.1%), with 50 patients (9.5%) being Grade  $\geq 3$ , in the integrated analysis (Siegel *et al*, 2013). However, in the present study, regarding Grade  $\geq 3$  cardiac AEs, only one (2.0%) patient in the 20 mg/m<sup>2</sup> cohort had cardiomyopathy, and no deaths occurred. Cardiotoxicities have been unexpectedly induced by PIs (Voortman & Giaccone, 2006; Orciuolo *et al*, 2007). In addition, unexplained deaths have been reported in the single-agent bortezomib study, which were attributed to CHF and sudden death, although they were regarded as probably not related to bortezomib (Richardson *et al*, 2009).

The previous integrated analysis reported that HT was documented in 14.3% and that more than half of those had a history of HT (Siegel *et al*, 2013). Although HT was more frequently recorded in our study (10 of 50 enrolled patients; 20%) than in the previous studies, four of the 10 patients were newly induced; however, in the remaining six patients who were prescribed hypertensive drugs before enrolment (Table SIV), HT was aggravated after carfilzomib treatment. As PIs have a potential to exacerbate impaired hypertensive states, blood pressure should be carefully monitored during the treatment, particularly in those who have a history of HT, and should be strictly controlled with additional anti-hypertensive drugs during carfilzomib treatment. It is noteworthy that there was a case reported in which the female patient developed severe CHF after bortezomib treatment, for which HT was the sole cardiovascular risk factor



(Bockorny *et al*, 2012); hence, we highlight this point. Moreover, intriguingly, in pressure-overload hearts of mice, it has been shown that proteasome activities in cardiomyocytes were depressed, resulting from cardiomyocyte apoptosis through the accumulation of pro-apoptotic proteins caused by impaired degradation, before the onset of cardiac dysfunction (Tsukamoto *et al*, 2006). Therefore, there is a great need for the pre-control of HT to mitigate the risk of cardiac toxicity, including heart failure, and control of HT is likely to be an important component of the successful management of MM patients treated with PIs.

GI disorders are caused by bortezomib; however, the rate of GI disorders was 21% lower for the subcutaneous administration of bortezomib than for intravenous administration, of which the incidence of diarrhoea was 12% lower (Moreau *et al*, 2011). The GI disorders may be ascribed to autonomic neuropathy (Mele *et al*, 2015) because it is a well-known fact that autonomic neuropathy is induced by bortezomib (Shah *et al*, 2004; Giannoccaro *et al*, 2011; Stratogianni *et al*, 2012; Mele *et al*, 2015); therefore, autonomic neuropathy may also account for PI-induced HT.

Although 222 (42.2%) and 67 (1.7%) patients experienced dyspnoea and pneumonia of any grade, respectively, in the integrated analysis (Siegel *et al*, 2013), only one (2.0%) and two (4.0%) of the patients in the present study experienced dyspnoea and pneumonia of any grade, respectively (Table V). The aetiology of dyspnoea remained unknown (Siegel *et al*, 2012) and has been debated (Siegel *et al*, 2013) because ILD was scarcely reported with regard to carfilzomib. Therefore, although dyspnoea was considered as pulmonary toxicity in the previous report (Siegel *et al*, 2013), it is more likely a symptom caused by pulmonary oedema owing to reversible acute left ventricular failure induced by PIs because it has been reported as a transient symptom that appeared on the day of or the day after carfilzomib dosing (Siegel *et al*, 2013). Consequently, in the present study, similar to a recent report (Sonneveld *et al*, 2015), we assumed dyspnoea to be a cardiovascular disorder (Table V) so that they would not be underestimated.

If carfilzomib can replace bortezomib as the mainstay of triple combination therapy (Jakubowiak *et al*, 2012; Niesvizky *et al*, 2013; Wang *et al*, 2013; Bringhen *et al*, 2014; Sonneveld *et al*, 2015; Stewart *et al*, 2015), it may be necessary to optimize the use of carfilzomib, although carfilzomib and lenalidomide combined with dexamethasone has an extremely compelling efficacy and is well tolerated (Stewart *et al*, 2015). To explain this, illustrative results of phase 1 or 2 carfilzomib trials using combination therapies were as follows: 1) a total of 33% of patients required carfilzomib dose reduction and 20% discontinued treatment because of AEs in combination with cyclophosphamide and dexamethasone for patients with newly diagnosed MM (Bringhen *et al*, 2014), 2) notably, a total of 31% of the patients enrolled in a dose-escalating study (up to 56 mg/m<sup>2</sup>) of carfilzomib experienced at least one Grade  $\geq 3$  dyspnoea when combined

with 300 mg/m<sup>2</sup> of cyclophosphamide and low-dose dexamethasone (Bensinger *et al*, 2014) and 3) furthermore, the rate of any cardiac-related AEs increased up to 19% with 5% Grade 3 after consolidation therapy following autologous stem cell transplantation in a phase 2 study, in which combination of carfilzomib, thalidomide and dexamethasone was used (Sonneveld *et al*, 2015). In this study, notably, only 59% of the patients were able to complete the original treatment schedule without either delays, reductions, interruptions or premature stoppage of carfilzomib during the induction therapy. Furthermore, a slower (30 min) infusion of carfilzomib was better tolerated and permitted the administration of higher doses (20/45 mg/m<sup>2</sup> or 20/56 mg/m<sup>2</sup>) according to the dissociation constant (K<sub>d</sub>); however, higher incidences of AEs were reported, including cough (40.9%), dyspnoea (31.8%) and HT (31.8%), with 13.6% of Grade  $\geq 3$  as the most common non-haematological Grade  $\geq 3$  AE (Badros *et al*, 2013).

Moreover, because our study showed that lymphopenia was the most common (Grade  $\geq 3$ , 68%), haematological AE (Table SI), in addition to upper respiratory disease being the most common reason for interruption of the treatment, additional care should be taken should carfilzomib be introduced into combination therapy in the future, particularly with pomalidomide and dexamethasone.

Lessons have been learned regarding the optimal administration of PIs from experiences with the use of the first-generation PI, bortezomib. Supportive care to avoid or prevent AEs induced by bortezomib and carfilzomib is important in continuous treatment with PIs (Delforge *et al*, 2010; Siegel, 2013). MM eventually develops resistance to all existing available therapies, and patients succumb to the disease (Kumar *et al*, 2012). Therefore, it is important to judiciously use PIs to reduce toxicities and to maintain the drug efficacy against currently existing MM in patients through a consecutive treatment of patients with MM through their life. To optimize the dose of carfilzomib, prescribing prophylactic drugs in advance for potential AEs in its earliest stages when toxicities are anticipated will be crucial for patients with MM to continue carfilzomib treatment and achieve more profound responses, which should prolong survival (Chanan-Khan & Giralt, 2010; Gay *et al*, 2011; Martínez-López *et al*, 2013).

In conclusion, in terms of safety, we did not find any clinically important ethnic differences in safety when carfilzomib was administered in a 20/27 mg/m<sup>2</sup> dosing regimen in Japanese MM patients. Although the PN rates with carfilzomib are low, it may worsen pre-existing PN. Cardiotoxicities were the major concern in previous carfilzomib studies, but they were less frequently observed in the present study; hypertensive status seemed to be exacerbated by the administration of carfilzomib and bortezomib, an affect that may be caused by PI-induced autonomic neuropathy. Therefore, we highlight the importance of managing AEs, including HT, by early treatment to alleviate PI-induced AEs so that

PI treatment can continue. With respect to efficacy, Japanese patients with RRMM achieved relatively longer PFS after higher total doses of carfilzomib than those administered in previous studies.

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## Author contributions

T. Watanabe performed the research and wrote this manuscript. Y. Shumiya and T. Kashihara designed the protocol and wrote the draft manuscript. K. Tobinai, M. Matsumoto, K. Suzuki, K. Sunami, T. Ishida, K. Ando, T. Chou, S. Ozaki, M. Taniwaki, N. Uike, H. Shibayama, K. Hatake, K. Izutsu, T. Ishikawa and S. Iida performed the research and contributed to the final version of the manuscript.

## Conflict of interest

The authors declare the following: TW: personal fees from Celgene. K.K., Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., Eisai Co., Ltd., Nippon Shinyaku Co., Ltd., Daiichi Sankyo Co., Ltd., Zenyaku Kogyo Co., Ltd., outside the submitted work. KT: grants from Ono Pharmaceutical Co., Ltd., during the conduct of the study; grants and other funding from Eisai and Takeda; grants from Chugai Pharma, Kyowa Hakko Kirin, Celgene, Janssen Pharmaceuticals, GlaxoSmithKline,

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table SI.** Adverse events ( $\geq 20\%$ ) of all grades or  $\geq$ Grade 3.

**Table SII.** Adverse events attributable to autonomic neuropathy.

**Table SIII.** Pharmacokinetic parameters.

**Table SIV.** Adverse event of hypertension.

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