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Carfilzomib, lenalidomide and dexamethasone in patients with heavily pretreated multiple myeloma: A phase 1 study in Japan

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Key words
carfilzomib, dexamethasone, Japan, lenalidomide, multiple myeloma

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This is the first study in which the carfilzomib, lenalidomide and dexamethasone (KRd) regimen was evaluated in heavily pretreated multiple myeloma. This study is a multicenter, open-label phase 1 study of KRd in Japanese patients with relapsed or refractory multiple myeloma (RRMM) patients. The objectives were to evaluate the safety, tolerability, efficacy and pharmacokinetics of the regimen. Carfilzomib was administrated intravenously over 10 min on days 1, 2, 8, 9, 15 and 16 of a 28-day cycle. In cycle 1, the dosage for days 1 and 2 was 20 mg/m^2, followed by 27 mg/m^2. Lenalidomide and dexamethasone were administered at 25 mg (days 1–21) and 40 mg (days 1, 8, 15 and 22), respectively. Twenty-six patients were enrolled. Patients had received a median of four prior regimens and 88.5% and 61.5% received previous bortezomib and lenalidomide, respectively. High-risk cytogenetics were seen in 53.8% of patients. The overall response rate was 88.5%. A higher rate of hyperglycemia was observed than in a previous carfilzomib monotherapy study, but this was attributed to dexamethasone. Carfilzomib pharmacokinetics were not affected by lenalidomide and dexamethasone. The KRd regimen was well tolerated and showed efficacy in Japanese RRMM patients.

Survival rates for patients with multiple myeloma have improved, but relapse remains common,[1,2] indicating that there is an ongoing need for novel therapeutic approaches. Having demonstrated improved progression-free survival (PFS) compared with dexamethasone alone, dexamethasone in combination with the immunomodulatory agent lenalidomide is now considered a standard therapy for newly diagnosed and relapsed multiple myeloma.[3]

Carfilzomib is a next-generation proteasome inhibitor that binds selectively and irreversibly to the constitutive proteasome and immunoproteasome, leading to sustained inhibition.[4] The ASPIRE study was a pivotal phase 3 study investigating the use of carfilzomib in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma who had received one to three prior treatments.[5] Overall, 792 patients were randomized to receive either carfilzomib with lenalidomide and dexamethasone or lenalidomide and dexamethasone alone. At the interim analysis, it was shown that the addition of carfilzomib resulted in significantly improved PFS.

On the basis of the ASPIRE study, carfilzomib in combination with lenalidomide and dexamethasone has recently been approved for use in Europe and the USA in patients with relapsed multiple myeloma.

The recent ENDEAVOR study compared carfilzomib plus dexamethasone with bortezomib plus dexamethasone in a head-to-head randomized trial in relapsed or refractory multiple myeloma (RRMM) patients.[6] Patients receiving carfilzomib and dexamethasone demonstrated longer PFS compared with those receiving bortezomib and dexamethasone, supporting evidence for the role of carfilzomib regimens in RRMM treatment.

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A recently published study investigated carfilzomib monotherapy in Japanese patients with RRMM.[7] This phase 1/2 study investigated the safety, pharmacokinetics/pharmacodynamics and overall response rate (ORR) at a dose of 20/27 mg/m^2. It demonstrated efficacy and tolerability, although the authors indicated that control of hypertension may be necessary with carfilzomib use.

The objectives of the present study were to evaluate the safety, tolerability, efficacy and pharmacokinetics of carfilzomib in combination with lenalidomide and dexamethasone in Japanese patients with RRMM, and to explore the efficacy of this combination regimen and the pharmacokinetic profile of carfilzomib.

Patients and Methods

Study design and setting. This was a multicenter, open-label phase 1 study in Japanese patients with RRMM. The study was conducted in nine centers in Japan. Patients were enrolled between November 2014 and March 2015 and the date of data cut-off was 8 July 2015.

Participants. The study enrolled male and female patients aged ≥20 years with RRMM and an Eastern Cooperative Oncology Group performance status of 0–2, and those who had received at least one prior treatment. Patients previously treated with lenalidomide and dexamethasone were eligible if they demonstrated tolerability to the therapy. Patients had to have adequate cardiovascular, hepatic, hematological and renal function (measured as creatinine clearance ≥50 mL/min) at screening. Those with grade 3 or 4 peripheral neuropathy (or grade 2 with pain) or New York Heart Association class III or IV heart failure at screening were excluded from the study. Pregnant or lactating females were excluded from participating. Furthermore, women of childbearing potential and men had to agree to use two forms of contraception from the start of the study until at least 3 months after the last dose of any of the three drugs used in the study.

Interventions. Treatment comprised a maximum of 18 cycles, with each cycle lasting 28 days. During cycles 1–12, carfilzomib was administered as a 10-min intravenous infusion on days 1, 2, 8, 9, 15 and 16. Patients received a starting dosage of 20 mg/m^2 carfilzomib on days 1 and 2 of the first cycle, and a target dose of 27 mg/m^2 thereafter. During cycles 13–18, carfilzomib was administered on days 1, 2, 15 and 16. The study drug was not administered beyond 18 cycles. The dosage regimen was selected based on the ASPIRE study.[5] Lenalidomide 25 mg was given orally on days 1–21 during cycles 1–18. The dose of lenalidomide was reduced if creatinine clearance was <50 mL/min. Dexamethasone 40 mg was given orally or intravenously on days 1, 8, 15 and 22 during cycles 1–18. If dexamethasone administration overlapped with carfilzomib, it was administered from 4 h to 30 min prior to carfilzomib administration. Patients received pre-treatment and post-treatment intravenous hydration (250–500 mL) during the first treatment cycle. Patients were also treated with antiviral and antithrombotic prophylaxis.

Endpoints. The transition rate to the extended treatment period (cycle 2 and thereafter) and adverse events (AE) meeting the criteria for evaluation of tolerability were assessed for the first six patients. The criteria for evaluation of tolerability were defined as any of the following AE in cycle 1 that were at least possibly related to carfilzomib, lenalidomide or dexamethasone: grade 3 or 4 peripheral neuropathy or grade 2 peripheral neuropathy with pain; grade ≥3 non-hematological toxicities; grade ≥3 nausea, vomiting or diarrhea that was uncontrolled after an adequate administration of anti-emetic or anti-diarrheal medications; grade ≥4 fatigue persisting for >7 days; grade 4 neutropenia persisting for >8 days; febrile neutropenia; grade 4 thrombocytopenia that required platelet transfusion or was accompanied by bleeding; and AE that required a dosing delay for >21 days.

Safety endpoints were assessed as AE, drug-related AE, general laboratory tests, vital signs and 12-lead electrocardiography. AE were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 18 (Japanese version), and tabulated by system organ class and preferred term (PT). Severity of AE was graded using the Common Terminology Criteria for Adverse Events (CTCAE).

Efficacy was assessed as ORR (partial response or better), overall survival (OS), PFS, time-to-progression (TTP), duration of response (DOR), best overall response, clinical benefit rate and disease control rate. Treatment responses and disease progression were assessed by investigators based on the central laboratory results. The efficacy and safety evaluation committee reviewed the investigator assessments.

Disease assessments were made with the use of the International Myeloma Working Group Uniform Response Criteria,[8,9] with minimal response defined according to European Society for Blood and Marrow Transplantation criteria.[10,11]

Bone marrow specimens for chromosome analysis were collected during screening. Chromosome analysis was performed using G-banding and fluorescence *in situ* hybridization, which was used to detect t(4;14), t(14;16) and t(11;14) translocations, and deletion of the short arm of chromosome 17 in ≥20% of screened plasma cells.

Plasma samples were collected on days 1 and 16 of cycle 1 at the following time points: pre-dose, 5 and 15 min after the start of infusion, the end of infusion, and 5, 15, 30, 60, 120 and 240 min post-infusion. Samples were processed by solid phase extraction using Oasis HLB 10-mg cartridges (Waters Corporation, Milford, MA, USA) followed by LC–MS/MS analysis to measure the plasma concentration of carfilzomib. A deuterated analog (d10-carfilzomib) was used as the internal standard for quantification, with a calibration range of 0.100–200 ng/mL. Chromatographic separation was achieved on a Gemini-NX C18 column (2.0 × 100 mm, 3-μm particle size; [Phenomenex, Torrance, USA]) and a linear gradient solvent system consisting of a methanol/water/25% ammonia solution. PK assessments included an estimation of the maximum plasma concentration (C_{max}), time to maximum plasma concentration, area under the plasma concentration-time curve (AUC), elimination half-life ($T_{1/2}$), systemic clearance (CL) and volume of distribution at steady state (V_{ss}).

Sample size. The sample size was determined as the number of subjects required for the evaluation of ORR, which was the efficacy endpoint. In the ASPIRE study,[5] the ORR was 87.1% (95% confidence interval [CI; Clopper–Pearson method] 83.4–90.3) in the carfilzomib, lenalidomide and dexamethasone group, and 66.7% (95% CI 61.8–71.3) in the lenalidomide and dexamethasone group. Under the expected ORR of 87.1%, the number of subjects required to reject the null hypothesis of 66.7% with at least 70% power based on a one-sided exact test with a significance level of 5.0% was calculated to be 25. Allowing for an estimated 4% of unevaluable subjects including dropouts, the target number of subjects for the study was determined as 26. The number of subjects for the evaluation of tolerability was determined as six, in line with the Guidelines for Clinical Evaluation Methods of Antimalignant Tumor Drugs.[12]

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Ethical considerations. The study was performed according to the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013) and was approved by the Institutional Review Board of each participating site. All participants provided written informed consent. The study was conducted in accordance with Japanese Good Clinical Practice Guidelines.

Statistical methods. *Safety.* Safety endpoints were analyzed in the safety analysis set. The numbers of patients with AE and drug-related AE, CTCAE grade ≥3 AE or drug-related AE, serious AE or drug-related AE, or those resulting in discontinuation were tabulated.

Efficacy. Efficacy endpoints were analyzed in the full analysis set. ORR and its 90% CI using the Clopper–Pearson method were calculated. Distributions of OS, PFS, TTP and DOR were presented using Kaplan–Meier curves.

Pharmacokinetics. Pharmacokinetic parameters were analyzed in the pharmacokinetic analysis set. Pharmacokinetic parameters were analyzed using summary statistics, and non-compartmental analysis was performed using Phoenix WinNonlin version 6.2.1 (Certara L.P., Princeton, NJ, USA).

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Twenty-six Japanese patients with RRMM were enrolled in the study. All 26 were included in the safety and efficacy analyses. The median number of cycles administered was four (range, 1–8 cycles). Patient baseline characteristics are summarized in Table 1. The median age was 64 years (range, 38–81 years), and the study included 13 women and 13 men. The median number of previous regimens received by study subjects was four (range, 1–10). Overall, 88.5% had received prior bortezomib therapy and 61.5% had received prior lenalidomide

Table 1. Patient demographics and baseline characteristics

Parameter	Category	KRd†	
Number of subjects		26	
Sex	Male	13	(50.0)
	Female	13	(50.0)
Age (years)	Median	64.0	
	Min–Max	38–81	
ECOG performance status	0	16	(61.5)
	1	9	(34.6)
	2	1	(3.8)
Subtype	IgGκ	17	(65.4)
	IgGλ	2	(7.7)
	IgAκ	4	(15.4)
	BJPκ	3	(11.5)
Stage (ISS)	1	11	(42.3)
	2	10	(38.5)
	3	5	(19.2)
Peripheral neuropathy‡	Grade 0	13	(50.0)
	Grade 1	10	(38.5)
	Grade 2	2	(7.7)
	Missing	1	(3.8)
Number of prior regimens by subject	1	5	(19.2)
	2	4	(15.4)
	3	3	(11.5)
	≥4	14	(53.8)
	Median	4.0	
	Min–Max	1–10	
Number of prior bortezomib treatments	0	3	(11.5)
	1	12	(46.2)
	≥2	11	(42.3)
Prior lenalidomide treatment	Yes	16	(61.5)
	No	10	(38.5)
Prior thalidomide treatment	Yes	8	(30.8)
	No	18	(69.2)
Prior corticosteroid treatment	Yes	26	(100.0)
	No	0	
High-risk cytogenetics§	Yes	14	(53.8)
	No	12	(46.2)
t(4;14)	Negative	18	(69.2)
	Positive	8	(30.8)
t(14;16)	Negative	24	(92.3)
	Positive	2	(7.7)
del(17p)	Negative	24	(92.3)
	Positive	2	(7.7)
G-band method (hypodiploidy)	Normal	23	(88.5)
	Abnormal	3	(11.5)
Creatinine clearance (mL/min)	<50	4	(15.4)
	50 to <80	9	(34.6)
	≥80	13	(50.0)
	Mean ± SD	81.109 ± 29.028	

†Figures in parentheses indicate percentages. ‡In cases of multiple neuropathy, the highest grade is used. §High-risk cytogenetics are defined as positive t(4;14), t(14;16) or del(17p) in ≥20% of screened plasma cells, or hypodiploidy with the G-band method. BJP, Bence Jones protein; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; KRd, carfilzomib + lenalidomide + dexamethasone regimen; SD, standard deviation.

Table 2. All grade AE and drug-related AE occurring in ≥20% of subjects

AE (SOC•PT)†	KRd			
	AE [*n* (%)]		Drug-related AE [*n* (%)]	
Number of subjects	26		26	
All	26	(100.0)	26	(100.0)
Gastrointestinal disorders	14	(53.8)	12	(46.2)
Constipation	8	(30.8)	6	(23.1)
Investigations	24	(92.3)	24	(92.3)
Alanine aminotransferase increased	7	(26.9)	7	(26.9)
Lymphocyte count decreased	14	(53.8)	11	(42.3)
Neutrophil count decreased	7	(26.9)	4	(15.4)
Platelet count decreased	14	(53.8)	12	(46.2)
White blood cell count decreased	8	(30.8)	4	(15.4)
Metabolism and nutrition disorders	19	(73.1)	18	(69.2)
Hyperglycemia	10	(38.5)	10	(38.5)
Hypophosphatemia	10	(38.5)	5	(19.2)
Musculoskeletal and connective tissue disorders	7	(26.9)	6	(23.1)
Muscle spasms	6	(23.1)	6	(23.1)
Skin and subcutaneous tissue disorders	11	(42.3)	9	(34.6)
Rash	8	(30.8)	7	(26.9)

†Medical Dictionary for Regulatory Activities Version 18.0 (Japanese version). AE, adverse events; KRd, carfilzomib + lenalidomide + dexamethasone regimen; PT, preferred term; SOC, system organ class.

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Table 3. Grade ≥3 AE and drug-related AE occurring during the study

	KRd			
AE (SOC•PT)†	AE [*n* (%)]		Drug-related AE [*n* (%)]	
Number of subjects	26		26	
All	19	(73.1)	17	(65.4)
Blood and lymphatic system disorders	3	(11.5)	1	(3.8)
Anemia	3	(11.5)	1	(3.8)
Cardiac disorders	1	(3.8)	0	
Prinzmetal angina	1	(3.8)	0	
Eye disorders	1	(3.8)	0	
Age-related macular degeneration	1	(3.8)	0	
Hepatobiliary disorders	1	(3.8)	1	(3.8)
Hepatic function abnormal	1	(3.8)	1	(3.8)
Infections and infestations	2	(7.7)	2	(7.7)
Pneumonia	2	(7.7)	2	(7.7)
Upper respiratory tract infection	1	(3.8)	1	(3.8)
Respiratory tract infection	1	(3.8)	1	(3.8)
Investigations	14	(53.8)	11	(42.3)
Alanine aminotransferase increased	2	(7.7)	2	(7.7)
Aspartate aminotransferase increased	1	(3.8)	1	(3.8)
Hemoglobin decreased	1	(3.8)	1	(3.8)
Lymphocyte count decreased	11	(42.3)	8	(30.8)
Neutrophil count decreased	3	(11.5)	3	(11.5)
Platelet count decreased	6	(23.1)	4	(15.4)
White blood cell count decreased	3	(11.5)	1	(3.8)
Metabolism and nutrition disorders	9	(34.6)	7	(26.9)
Hyperglycemia	3	(11.5)	3	(11.5)
Hypermagnesemia	1	(3.8)	0	
Hypokalemia	1	(3.8)	1	(3.8)
Hypophosphatemia	5	(19.2)	3	(11.5)
Psychiatric disorders	1	(3.8)	1	(3.8)
Delirium	1	(3.8)	1	(3.8)
Skin and subcutaneous tissue disorders	2	(7.7)	1	(3.8)
Drug eruption	1	(3.8)	0	
Rash	1	(3.8)	1	(3.8)

†Medical Dictionary for Regulatory Activities Version 18.0 (Japanese version). AE, adverse events; KRd, carfilzomib + lenalidomide + dexamethasone regimen; PT, preferred term; SOC, system organ class.

Table 4. Best anti-tumor effect (International Myeloma Working Group Uniform Response Criteria)

Response	*N* (%)
Number of subjects	26
Stringent complete response	0
Complete response	1 (3.8)
Very good partial response	5 (19.2)
Partial response	17 (65.4)
Minimal response	1 (3.8)
Stable disease†	2 (7.7)
Progressive disease	0
Not evaluable	0

†Patients who were assessed as having stable disease according to the International Myeloma Working Group. Of these, patients who were assessed as having minimal response in accordance with the European Society for Blood and Marrow Transplantation were excluded.

therapy. A total of 53.8% of patients had high-risk abnormal cytogenetics, defined as t(4;14), t(14;16), del(17p) in ≥20% of screened plasma cells, or hypodiploidy.

Safety findings. One patient out of six evaluated for tolerability experienced grade 3 upper respiratory tract infection, which met the definition of AE for the evaluation of tolerability. No other subjects experienced AE for the evaluation of tolerability. All patients experienced at least one AE, and 73.1% had at least one AE of CTCAE grade ≥3. AE are summarized in Tables 2 and 3. The most common AE (summarized by MedDRA PT) included decreased lymphocyte count (53.8%), decreased platelet count (53.8%), hyperglycemia (38.5%), hypophosphatemia (38.5%), constipation (30.8%), decreased white blood cell count (30.8%) and rash (30.8%; Table 2).

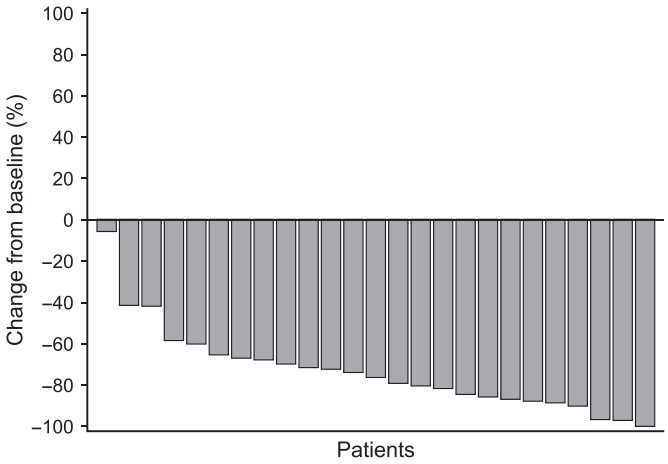

Fig. 1. Waterfall plot showing the maximum percentage change in the amount of M-protein for each patient. Data are not shown for one patient because of a limited number of time points where M-protein was measurable.

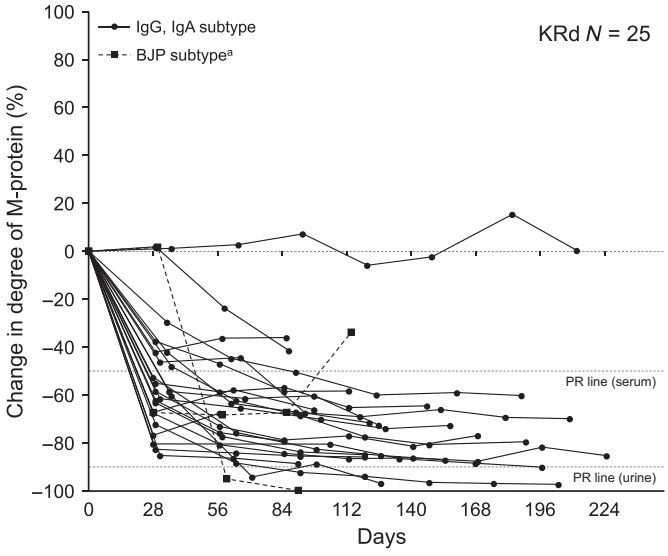

Fig. 2. Change in M-protein over time for each patient. Data are not shown for 1 patient because of a limited number of time points where M-protein was measurable. [a]Urine M-protein. BJP, Bence Jones protein; KRd, carfilzomib + lenalidomide + dexamethasone regimen; PR, partial response.

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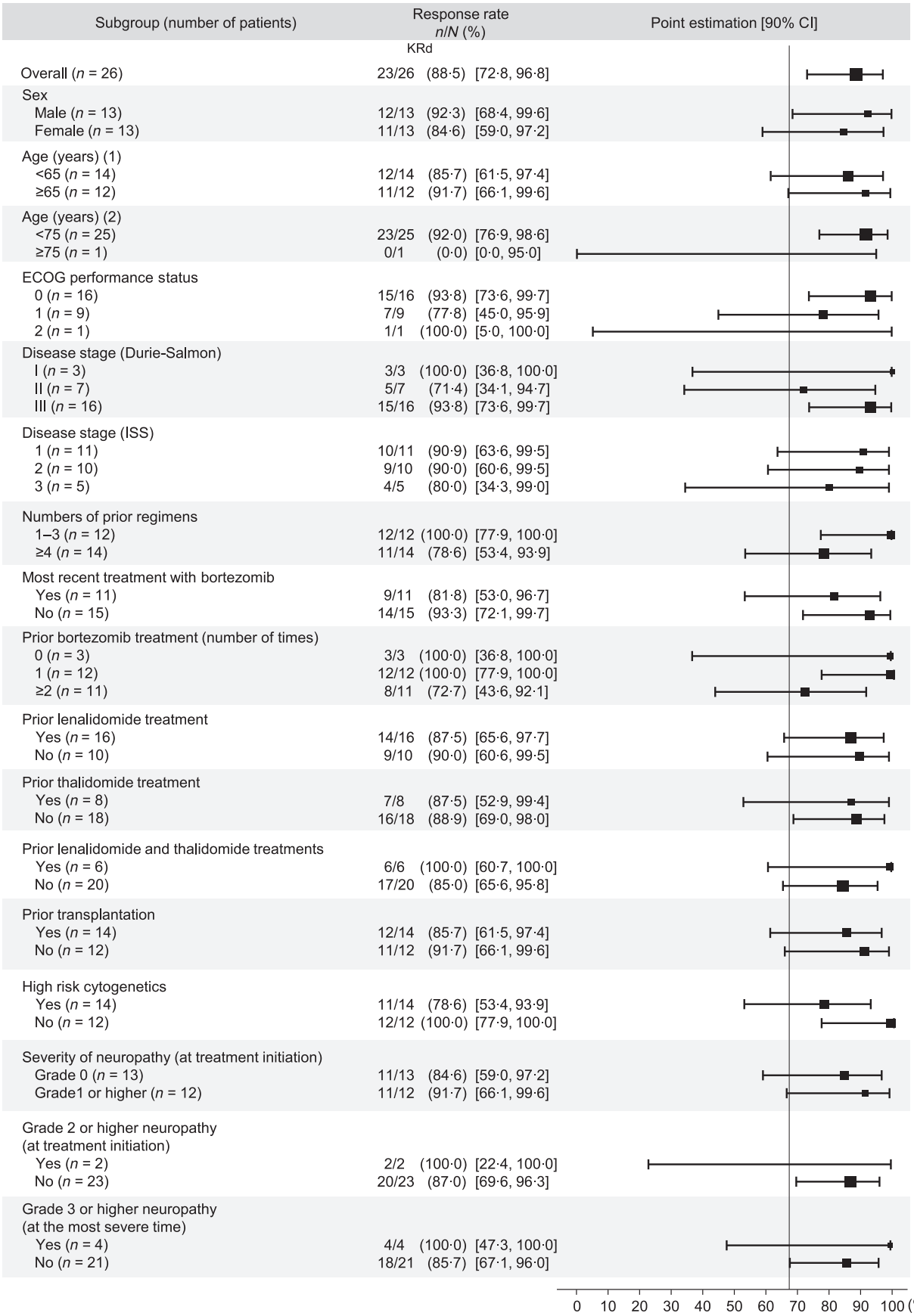

Fig. 3. Subgroup analysis for overall response rate. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; KRd, carfilzomib + lenalidomide + dexamethasone regimen.

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Table 5. Best response of individual patients included in the study

Patient	Best response	Subtype	Number of prior regimens	Number of Completed cycles	Chromosomal abnormalities	Risk
1	CR	BJPκ	1	4	t(11;14)	—
2	VGPR	IgAκ	9	7	t(4;14)	High
3	VGPR	IgGκ	7	4	Hypodiploid	High
4	VGPR	IgGκ	5	5	t(14;16)	High
5	VGPR	IgGκ	4	5	Hyperdiploid	—
6	VGPR	IgAκ	4	3	t(4;14)	High
7	PR	IgAκ	10	4	t(4;14), Hyperdiploid	High
8	PR	IgGκ	8	7	t(11;14)	—
9	PR	IgGκ	7	6	—	—
10	PR	IgGκ	6	5	—	—
11	PR	IgAκ	4	4	—	—
12	PR	IgGκ	4	4	t(4;14), Hypodiploid	High
13	PR	IgGκ	3	8	t(4;14), Hyperdiploid	High
14	PR	IgGκ	3	3	del(17p)	High
15	PR	BJPκ	3	3	t(11;14)	—
16	PR	IgGκ	2	5	—	—
17	PR	IgGλ	2	4	t(4;14)	High
18	PR	BJPκ	2	4	—	—
19	PR	IgGκ	2	1	t(11;14)	—
20	PR	IgGκ	1	6	—	—
21	PR	IgGκ	1	6	t(14;16)	High
22	PR	IgGκ	1	4	t(4;14)	High
23	PR	IgGκ	1	3	—	—
24	SD	IgGλ	10	7	del(17p)	High
25	SD	IgGκ	5	3	t(11;14), Hypodiploid	High
26	SD	IgGκ	4	3	t(4;14), Non-hyperdiploid	High

BJP, Bence Jones protein; CR, complete response; PR, partial response; SD, stable disease; VGPR, very good partial response.

The most common grade ≥3 AE were decreased lymphocyte count (42.3%), decreased platelet count (23.1%), hypophosphatemia (19.2%), anemia (11.5%), neutrophil count decreased (11.5%), decreased white blood cell count (11.5%) and hyperglycemia (11.5%; Table 3). Peripheral neuropathy was observed in 15.4% of patients, but no grade ≥3 peripheral neuropathy or peripheral neuropathy associated with pain was reported. Regarding cardiac disorders, 1 patient experienced grade 2 congestive cardiac failure, which led to dose interruption of carfilzomib. One patient experienced grade 3 Prinzmetal angina, but this was not considered to be related to carfilzomib because the patient had a medical history of Prinzmetal angina and did not receive treatment for Prinzmetal angina when the event occurred. No interstitial lung disease was observed during the study, and no patients died during the treatment period or within 30 days after the last dose of any of the three drugs.

Regarding serious AE, grade 4 pneumonia and grade 3 respiratory tract infection developed in one patient, who recovered following treatment. A causal relationship with any of the three drugs could not be ruled out. One patient developed delirium, which led to treatment discontinuation. The investigator considered the event of delirium to be related to dexamethasone. There were no other AE that led to treatment discontinuation. AE that led to interruption or dose reduction of carfilzomib occurred in 46.2% of patients, with events occurring in two or more patients including pneumonia (11.5%), upper respiratory tract inflammation (11.5%), pharyngitis (7.7%) and hypophosphatemia (7.7%).

Efficacy findings. The ORR during the study was 88.5% (90% CI 72.8–96.8). The lower end of this CI rejected the null hypothesis of 66.7%. Tumor response is shown in Table 4, and the maximum percentage change in the amount of M-protein, and the change in M-protein level stratified by Bence Jones protein (BJP) and non-BJP subtype for each patient are shown in Figures 1 and 2, respectively. The rate of very good partial response or better was 23.1%. The ORR benefit of KRd was consistently observed in all subgroups (Fig. 3). Overall, 7/8 (87.5%), 2/2 (100%), 1/2 (50.0%) and 2/3 (66.7%) patients with t(4:14), t(14;16), del(17p) or hypodiploid cytogenetics, respectively, demonstrated good ORR (Table 5). The median time to best response was 63 days (range, 28–168 days; $n = 23$ responders). The median PFS, OS, TTP and DOR could not be estimated because of the short follow-up period of the study.

Pharmacokinetic findings. Eleven patients were included in the pharmacokinetic analysis set. The pharmacokinetic parameters of carfilzomib on days 1 and 16 of the first cycle are summarized in Table 6. The carfilzomib plasma concentration declined quickly at both doses following intravenous administration (Fig. 4). $T_{1/2}$ ranged from 0.58 to 0.74 h. C_{max} and AUC_{INF} increased dose-dependently, whereas CL and V_{ss} were comparable at both doses.

Discussion

This is the first study to investigate the use of the carfilzomib, lenalidomide and dexamethasone regimen in heavily pretreated RRMM patients, with patients having received a median of four prior regimens. The regimen was well tolerated and demonstrated early indications of efficacy in this group of Japanese RRMM patients.

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Table 6. Pharmacokinetic parameters of carfilzomib on days 1 and 16 of the first cycle

Parameter	Plasma carfilzomib†	
	20 mg/m^2 (day 1)	27 mg/m^2 (day 16)
Number of patients	11	9
C_{max} (ng/mL)	1540 ± 391	2030 ± 282
T_{max} (h)‡	0.150 (0.083–0.167)	0.150 (0.133–0.183)
AUC_{LAST} (ng*h/mL)	326 ± 73.5	444 ± 56.0
AUC_{INF} (ng*h/mL)	326 ± 73.5	445 ± 55.7
$T_{1/2}$ (h)	0.580 ± 0.260	0.740 ± 0.272
CL (L/h)	102 ± 27.3	98.8 ± 16.1
V_{ss} (L)	10.9 ± 4.39	11.7 ± 5.40

†All values are mean ± standard deviation unless stated otherwise.
‡Median (min–max). AUC, area under the plasma concentration-time curve; CL, systemic clearance; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $T_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady-state.

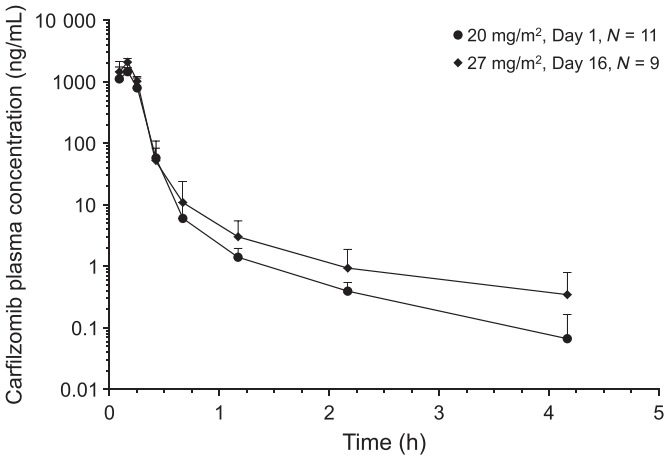

Fig. 4. Carfilzomib plasma concentration-time profile following a 10-min intravenous infusion of carfilzomib (mean + standard deviation; first cycle).

The phase 3 ASPIRE study also examined the use of carfilzomib in combination with lenalidomide and dexamethasone.[5] The ORR was similar between the current study and the ASPIRE study (88.5% and 87.1%, respectively), while the current study enrolled patients at a later stage, with a median of four prior regimens having been used compared with a median of two in ASPIRE. However, the rate of very good partial response or better was lower in this study compared with ASPIRE (23.1% and 69.9%, respectively). This may have been a result of the lower number of cycles administered (median of four in the current study versus 18 in ASPIRE). The current study showed a ≥15% higher incidence of decreased lymphocyte count (53.8% and <20%, respectively), decreased platelet count (53.8% and <20%, respectively), hyperglycemia (38.5% and <20%, respectively) and hypophosphatemia (38.5% and <20%, respectively) compared with the ASPIRE study.

Ixazomib, elotuzumab and daratumumab have also been recently approved for use in multiple myeloma. Similar to the current study, Moreau *et al.*[13] compared the use of the proteasome inhibitor ixazomib in combination with lenalidomide plus dexamethasone with placebo and lenalidomide plus dexamethasone. ORR was 78.3% in the ixazomib group, which is lower than that reported in the current study, although a cross-study comparison is difficult. The monoclonal antibody elotuzumab was also examined in a similar regimen (elotuzumab plus lenalidomide and dexamethasone compared with lenalidomide and dexamethasone alone).[14] The elotuzumab regimen also showed a slightly lower ORR (79%) than the current study, providing further support for the use of the carfilzomib plus lenalidomide and dexamethasone regimen. Interim data from a phase 3 study by Dimopoulos *et al.*[15] showed a comparable ORR for the daratumumab plus lenalidomide and dexamethasone regimen (93%) to that observed in the current study.

Watanabe *et al.*[7] recently conducted a phase 1/2 study of carfilzomib monotherapy in Japanese RRMM patients. The ORR of 88.5% in the current study was significantly higher than that observed in the monotherapy study (22.5%). Regarding AE, a higher rate of hyperglycemia was observed in the current study compared with the monotherapy study, but this is thought to be attributable to the addition of dexamethasone. No other clinically important differences in safety profile were observed with the carfilzomib, lenalidomide and dexamethasone regimen compared with carfilzomib monotherapy. One patient out of six evaluated for tolerability experienced grade 3 upper respiratory tract infection, supporting early evidence of the tolerability of the regimen in this cohort of Japanese patients. The pharmacokinetic profile of carfilzomib did not appear to be affected by the addition of lenalidomide and dexamethasone.

A potential weakness of the current study is that PFS and OS could not be determined because of the short follow-up period. However, the study is ongoing and further survival data, including PFS and OS, are to be reported in the near future. A strength of the study is that a relatively high percentage of patients with abnormal cytogenetics were enrolled (53.8% compared with 12.1% in the ASPIRE study), with the combination regimen showing efficacy in this high-risk population.

In conclusion, in this cohort of Japanese RRMM patients, the addition of carfilzomib to lenalidomide and dexamethasone resulted in improved ORR, and the benefit–risk profile appeared to be favorable. These findings indicate that the use of the carfilzomib, lenalidomide and dexamethasone regimen in RRMM patients is promising in this population, consistent with earlier results from the ASPIRE study.

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