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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Funding Information
T. Chou received honoraria from Ono Pharmaceutical and Celgene K.K. T. Ishida received personal fees from Celgene K.K. T. Izumi, M. Ri, I. Sugiura, K. Sunami, K. Suzuki and S. Ozaki received research funding from Ono Pharmaceutical K. Sunami received research funding from Celgene K.K. S. Iida received honoraria from Ono Pharmaceutical and Celgene K.K. The study was funded by Ono Pharmaceutical. Carfilzomib was provided by Ono Pharmaceutical.

Clinical trial registration: Japic CTI 142677

Received October 12, 2016; Revised December 27, 2016; Accepted January 6, 2017

Cancer Sci 108 (2017) 461–468
doi: 10.1111/cas.13166

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.
A recently published study investigated carfilzomib monotherapy in Japanese patients with RRMM. This phase 1/2 study investigated the safety, pharmacokinetics/pharmacodynamics and overall response rate (ORR) at a dose of 20/27 mg/m². 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 who 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/m² carfilzomib on days 1 and 2 of the first cycle, and a target dose of 27 mg/m² 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. 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; leucocyte 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.

**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 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 un evaluable 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.
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 | IgGk | 17 (63.4) |
| | IgGλ | 2 (7.7) |
| | IgAλ | 4 (15.4) |
| | BJP | 3 (11.5) |
| Stage (ISS) | Grade 0 | 11 (42.3) |
| | Grade 1 | 10 (38.5) |
| | Grade 2 | 2 (7.7) |
| Peripheral neuropathy† | Missing | 1 (3.8) |
| Number of prior regimens | 1 | 5 (19.2) |
| by subject | 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

| Parameter | Category | KRd† |
|-----------|----------|------|
| AE (SOC-PT)† | | |
| Number of subjects | 26 | |
| All | 26 (100.0) |
| Gastrointestinal disorders | 14 (53.8) |
| Constipation | 8 (30.8) |
| Investigations | 24 (92.3) |
| Alanine aminotransferase increased | 7 (26.9) |
| Lymphocyte count decreased | 14 (53.8) |
| Neutrophil count decreased | 7 (26.9) |
| Platelet count decreased | 14 (53.8) |
| White blood cell count decreased | 8 (30.8) |
| Metabolism and nutrition disorders | 19 (73.1) |
| Hypoglycemia | 10 (38.5) |
| Hypophosphatemia | 10 (38.5) |
| Musculoskeletal and connective tissue disorders | 7 (26.9) |
| Muscle spasms | 6 (23.1) |
| Skin and subcutaneous tissue disorders | 11 (42.3) |
| Rash | 8 (30.8) |

†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.
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).

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

| 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.

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 one patient because of a limited number of time points where M-protein was measurable.
### Subgroup analysis for overall response rate

| Subgroup (number of patients)                              | Response rate n/N (%) | Point estimation [90% CI] |
|------------------------------------------------------------|------------------------|----------------------------|
| Overall (n = 26)                                           | 23/26 (88.5) [72.8, 96.8] |                            |
| **Sex**                                                    |                        |                            |
| Male (n = 13)                                              | 12/13 (92.3) [68.4, 99.6] |                            |
| Female (n = 13)                                            | 11/13 (84.6) [59.0, 97.2] |                            |
| **Age (years)**                                            |                        |                            |
| <65 (n = 14)                                               | 12/14 (85.7) [61.5, 97.4] |                            |
| ≥65 (n = 12)                                               | 11/12 (91.7) [66.1, 99.6] |                            |
| **Age (years)**                                            |                        |                            |
| <75 (n = 25)                                               | 23/25 (92.0) [76.9, 98.6] |                            |
| ≥75 (n = 1)                                                | 0/1 (0.0) [0.0, 95.0]    |                            |
| **ECOG performance status**                               |                        |                            |
| 0 (n = 16)                                                 | 15/16 (93.8) [73.6, 99.7] |                            |
| 1 (n = 9)                                                  | 7/9 (77.8) [45.0, 95.9]  |                            |
| 2 (n = 1)                                                  | 1/1 (100.0) [5.0, 100.0] |                            |
| **Disease stage (Durie-Salmon)**                           |                        |                            |
| I (n = 5)                                                  | 3/3 (100.0) [36.8, 100.0] |                            |
| II (n = 7)                                                 | 5/7 (71.4) [34.1, 94.7]  |                            |
| III (n = 16)                                               | 15/16 (93.8) [73.6, 99.7] |                            |
| **Disease stage (ISS)**                                    |                        |                            |
| 1 (n = 11)                                                 | 10/11 (90.9) [63.6, 99.6] |                            |
| 2 (n = 10)                                                 | 9/10 (90.0) [60.6, 99.5]  |                            |
| 3 (n = 5)                                                  | 4/5 (80.0) [34.3, 99.0]   |                            |
| **Numbers of prior regimens**                              |                        |                            |
| 1–3 (n = 12)                                               | 12/12 (100.0) [77.9, 100.0] |                        |
| ≥4 (n = 14)                                                | 11/14 (78.6) [53.4, 93.9] |                            |
| **Most recent treatment with bortezomib**                  |                        |                            |
| Yes (n = 11)                                               | 9/11 (81.8) [53.0, 96.7]  |                            |
| No (n = 15)                                                | 14/15 (93.3) [72.1, 99.7] |                            |
| **Prior bortezomib treatment (number of times)**           |                        |                            |
| 0 (n = 3)                                                  | 3/3 (100.0) [36.8, 100.0] |                            |
| 1 (n = 12)                                                 | 12/12 (100.0) [77.9, 100.0] |                        |
| ≥2 (n = 11)                                                | 8/11 (72.7) [43.6, 92.1]  |                            |
| **Prior lenalidomide treatment**                           |                        |                            |
| Yes (n = 16)                                               | 14/16 (87.5) [65.6, 97.7] |                            |
| No (n = 10)                                                | 9/10 (90.0) [60.6, 99.5]  |                            |
| **Prior thalidomide treatment**                            |                        |                            |
| Yes (n = 8)                                                | 7/8 (87.5) [52.9, 99.4]   |                            |
| No (n = 18)                                                | 16/18 (94.5) [69.0, 99.0] |                            |
| **Prior lenalidomide and thalidomide treatments**          |                        |                            |
| Yes (n = 6)                                                | 6/6 (100.0) [80.7, 100.0] |                            |
| No (n = 20)                                                | 17/20 (85.0) [65.6, 95.8] |                            |
| **Prior transplantation**                                  |                        |                            |
| Yes (n = 14)                                               | 12/14 (85.7) [61.5, 97.4] |                            |
| No (n = 12)                                                | 11/12 (91.7) [66.1, 99.6] |                            |
| **High risk cytogenetics**                                 |                        |                            |
| Yes (n = 14)                                               | 11/14 (78.6) [53.4, 93.9] |                            |
| No (n = 12)                                                | 12/12 (100.0) [77.9, 100.0] |                        |
| **Severity of neuropathy (at treatment initiation)**       |                        |                            |
| Grade 0 (n = 13)                                           | 11/13 (84.6) [59.0, 97.2] |                            |
| Grade 1 or higher (n = 12)                                 | 11/12 (91.7) [66.1, 99.6] |                            |
| **Grade 2 or higher neuropathy (at treatment initiation)** |                        |                            |
| Yes (n = 2)                                                | 2/2 (100.0) [22.4, 100.0]  |                            |
| No (n = 23)                                                | 20/23 (87.0) [69.6, 96.3]  |                            |
| **Grade 3 or higher neuropathy (at the most severe time)** |                        |                            |
| Yes (n = 4)                                                | 4/4 (100.0) [47.3, 100.0]  |                            |
| No (n = 21)                                                | 18/21 (85.7) [67.1, 96.0]  |                            |

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.
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 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). T1/2 ranged from 0.58 to 0.74 h. Cmax and AUCINF increased dose-dependently, whereas CL and Vss 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 5. Best response of individual patients included in the study**

| Patient | Best response | Subtype       | Number of completed cycles | Chromosomal abnormalities | Risk |
|---------|---------------|---------------|-----------------------------|---------------------------|------|
| 1       | CR            | BjP            | 4                           | t(11;14)                  | —    |
| 2       | VGPR          | IgA            | 7                           | t(4;14)                   | High |
| 3       | VGPR          | IgG            | 4                           | Hypodiploid              | High |
| 4       | VGPR          | IgG            | 5                           | t(14;16)                  | High |
| 5       | VGPR          | IgG            | 4                           | Hyperdiploid             | —    |
| 6       | VGPR          | IgA            | 3                           | t(4;14)                   | High |
| 7       | PR            | IgA            | 4                           | t(4;14)                   | High |
| 8       | PR            | IgG            | 7                           | t(11;14)                  | —    |
| 9       | PR            | IgG            | 6                           | —                          | —    |
| 10      | PR            | IgG            | 6                           | —                          | —    |
| 11      | PR            | IgA            | 4                           | —                          | —    |
| 12      | PR            | IgG            | 4                           | t(4;14)                   | High |
| 13      | PR            | IgG            | 8                           | t(4;14), Hyperdiploid     | High |
| 14      | PR            | IgG            | 3                           | del(17p)                  | High |
| 15      | PR            | BjP            | 3                           | t(11;14)                  | —    |
| 16      | PR            | IgG            | 2                           | 5                          | —    |
| 17      | PR            | IgG            | 2                           | t(4;14)                   | High |
| 18      | PR            | BjP            | 2                           | 4                          | —    |
| 19      | PR            | IgG            | 2                           | t(11;14)                  | —    |
| 20      | PR            | IgG            | 1                           | 6                          | —    |
| 21      | PR            | IgG            | 1                           | t(14;16)                  | High |
| 22      | PR            | IgG            | 1                           | t(4;14)                   | High |
| 23      | PR            | IgG            | 1                           | t(4;14)                   | High |
| 24      | SD            | IgG            | 10                          | del(17p)                  | High |
| 25      | SD            | IgG            | 5                           | t(11;14), Hyperdiploid    | High |
| 26      | SD            | IgG            | 4                           | 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 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 greater 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.

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.

Acknowledgments

We thank all study participants and their families, and all investigators, physicians, nurses, and clinical research coordinators who assisted with the study. We would also like to thank the medical consultant, Dr Hirokazu Murakami (Gunma University Graduate School of Health Science, Maebashi), and Dr Chihiro Shimazaki (Japan Community Health Care Organization Kyoto-Kuramaguchi Medical Center, Kyoto), Dr Masahiro Kizaki (Saitama Medical Center, Saitama Medical University, Saitama), Dr Takao Katoh (International University of Health and Welfare, Mita Hospital, Tokyo), Dr Masahiro Endo (Shizuoka Cancer Center, Nagaizumi) and Dr Terufumi Kato (Kanagawa Cancer Center, Yokohama) for their review of the clinical data as members of the Efficacy and Safety Evaluation Committee. We also acknowledge the statistical support of Naokazu Gion (Ono Pharmaceutical, Osaka) and critical review of the manuscript by Mike Kelsch, Sanjay Aggarwal, Sunhee Ro and Ying Ou (Amen, Thousand Oaks). Medical writing support was provided by Helen Robertson and Dr Sarah Williams.
Disclosure Statement

T. Chou received honoraria from Ono Pharmaceutical and Celgene K.K. T. Ishida received personal fees from Celgene K.K. T. Izumi, M. Ri, I. Sugii, K. Sunami, K. Suzuki and S. Ozaki received research funding from Ono Pharmaceutical K. Sunami received research funding from Celgene K.K. K. Ota and Y. Shumiya are employees of Ono Pharmaceutical. S. Iida received honoraria from Ono Pharmaceutical and Celgene K.K. Sunami. N. Takezako has no conflicts of interest to declare. The study was designed under the responsibility of Ono Pharmaceutical. The study was funded by Ono Pharmaceutical. Carfilzomib was provided by Ono Pharmaceutical. Ono Pharmaceutical collected and analyzed the data and contributed to the interpretation of the study. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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