

Phase I Study of 30-Minute Infusion of Carfilzomib As Single Agent or in Combination With Low-Dose Dexamethasone in Patients With Relapsed and/or Refractory Multiple Myeloma

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See accompanying article on page 782

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Published online ahead of print at www.jco.org on September 15, 2014.

Supported by Onyx Pharmaceuticals.

Presented in part at the 53rd Annual Meeting of the American Society of Hematology (ASH), San Diego, CA, December 10-13, 2011, 54th ASH Annual Meeting, Atlanta, GA, December 8-11, 2012, and 14th International Myeloma Workshop, Kyoto, Japan, April 3-7, 2013.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00531284.

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0732-183X/15/3307w-732w/\$20.00

DOI: 10.1200/JCO.2013.52.3522

ABSTRACT

Purpose

Carfilzomib is an irreversible inhibitor of the constitutive proteasome and immunoproteasome. This phase I study evaluated the maximum-tolerated dose (MTD), pharmacokinetics, and pharmacodynamics of carfilzomib administered as a 30-minute intravenous (IV) infusion. Safety and efficacy of carfilzomib as a single agent or in combination with low-dose dexamethasone were assessed.

Patients and Methods

Patients with relapsed and/or refractory multiple myeloma (MM) were administered single-agent carfilzomib on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Cycle one day 1 and 2 doses were 20 mg/m², followed thereafter by dose escalation to 36, 45, 56, or 70 mg/m². Additionally, carfilzomib was combined with low-dose dexamethasone (40 mg/wk).

Results

Thirty-three patients were treated with single-agent carfilzomib. Dose-limiting toxicities in two patients at 70 mg/m² were renal tubular necrosis and proteinuria (both grade 3). The MTD was 56 mg/m². Nausea (51.5%), fatigue (51.5%), pyrexia (42.4%), and dyspnea and thrombocytopenia (each 39.4%) were the most common treatment-related toxicities. Overall response rate (ORR) was 50% (56-mg/m² cohort). Increasing carfilzomib dosing from 20 to 56 mg/m² resulted in higher area under the plasma concentration-time curve from time zero to last sampling and maximum plasma concentration exposure with short half-life (range, 0.837 to 1.21 hours) and dose-dependent inhibition of proteasome chymotrypsin-like activity. In 22 patients treated with 45 or 56 mg/m² of carfilzomib plus low-dose dexamethasone, the ORR was 55% with a safety profile comparable to that of single-agent carfilzomib.

Conclusion

Carfilzomib administered as a 30-minute IV infusion at 56 mg/m² (as single agent or with low-dose dexamethasone) was generally well tolerated and highly active in patients with relapsed and/or refractory MM. These data have provided the basis for the phase III randomized, multicenter trial ENDEAVOR.

J Clin Oncol 33:732-739. © 2014 by American Society of Clinical Oncology

INTRODUCTION

In the last decade, there have been considerable advances in the treatment of multiple myeloma (MM), with the introduction of immunomodulatory agents (IMiDs) and the proteasome inhibitor bortezomib. Dexamethasone remains an integral part of antimyeloma regimens; at appropriate doses, it has improved the tolerability and efficacy of these agents.¹ Although survival has improved,² most patients will relapse, highlighting the need for more effective treatment.^{3,4}

Carfilzomib is an epoxyketone-based proteasome inhibitor that selectively and irreversibly inhibits chymotrypsin-like (CT-L) activities of the constitutive proteasome and immunoproteasome by a mechanism distinct from that of bortezomib.^{5,6} Carfilzomib was approved in the United States in 2012 for patients with MM who had received ≥ two prior therapies, including bortezomib and an IMiD.⁷ In the pivotal phase II study,⁸ single-agent carfilzomib was efficacious, with an acceptable safety and tolerability profile administered intravenously (IV) over 2 to 10 minutes at a dose of 20

mg/m² for cycle one and 27 mg/m² thereafter in patients with relapsed and/or refractory MM, with an overall response rate (ORR) of 23.7%.⁸ Notably, doses of carfilzomib > 27 mg/m² were not administered, and a maximum-tolerated dose (MTD) was not reached.⁹

Clinical evidence for carfilzomib dose response has been observed in a multivariable modeling analysis comparing 20 with 27 mg/m²,¹⁰ suggesting that more effective inhibition of proteasome activity may improve efficacy. P-glycoprotein overexpression seems to mediate resistance to carfilzomib in myeloma cell lines^{6,11}; however, the clinical relevance and whether increased dose can overcome this resistance are unknown. In preclinical in vivo models, carfilzomib potency seems to be a consequence of total dose administered rather than maximum plasma concentration (C_{max}), with higher C_{max} likely contributing to toxicity.¹² Dose-limiting toxicities (DLTs) of carfilzomib in rat studies included toxicity to bone marrow, renal, pulmonary, and cardiovas-

cular systems.^{12,13} A study in rats comparing 2- to 10-minute IV bolus infusions with 30-minute infusion at the same carfilzomib dose showed significantly lower C_{max} with the latter but equivalent proteasome inhibition and greatly improved tolerability, decreasing animal mortality from 44% to 0%.^{12,13} Preliminary dose-response data, combined with these preclinical safety results, suggest that a 30-minute infusion may be better tolerated and permit administration of higher doses than a 2- to 10-minute infusion, with the potential for increased proteasome inhibition and improved clinical efficacy.

The primary objectives of this phase I dose-escalation study were to evaluate the safety and tolerability of single-agent carfilzomib administered as a 30-minute infusion in patients with relapsed and/or refractory MM and to determine the MTD. Secondary objectives included evaluation of efficacy, pharmacokinetics (PKs), and pharmacodynamics (PDs). An amendment was performed to evaluate the

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	Single-Agent Carfilzomib				Carfilzomib Plus Low-Dose Dexamethasone	
	56 mg/m ² (n = 24)		Total (n = 33)		Total (n = 22)	
	No.	%	No.	%	No.	%
Sex						
Male	17	70.8	22	66.7	17	77.3
Age, years						
Median	63.5		65.0		59.5	
Range	45-81		45-81		41-72	
Years since diagnosis						
Median	5.4		4.7		3.6	
Range	1.1-11.5		1.1-11.5		0.6-8.5	
Heavy chain						
IgG	11	45.8	18	54.5	13	59.1
IgA	6	25.0	6	18.2	6	27.3
IgD	0	0.0	0	0.0	2	9.1
Not applicable*	7	29.2	9	27.3	1	4.5
ECOG performance status						
0	8	33.3	12	36.4	12	54.5
1-2	16	66.7	21	63.6	10	45.5
Cytogenetics or FISH						
Normal or standard risk	16	66.7	22	66.7	14	63.6
High risk†	6	25.0	7	21.2	7	31.8
Unknown or not done	2	8.3	4	12.1	1	4.5
No. of prior lines of therapy‡						
Median	5		5		4	
Range	2-9		1-9§		2-9	
No. of prior transplantations						
Median	1		1		1	
Range	0-3		0-3		1-2	
Prior therapy						
Bortezomib	23	95.8	30	90.9	21	95.5
IMiDs	24	100.0	31	93.9	22	100.0
Refractory status						
Bortezomib	18	75.0	22	66.7	11	50.0
Lenalidomide	20	83.3	25	75.8	10	45.5
Thalidomide	13	54.2	14	42.4	3	13.6
Last regimen	20	83.3	27	81.8	14	63.6

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FISH, fluorescent in situ hybridization; Ig, immunoglobulin; IMiD, immunomodulatory drug.

*Light chain–only disease.

†High risk by FISH: t(4;14), t(14;16), del(17p;13). High risk by cytogenetics: del(13q), t(4;14), t(14;16), del(17p;13).

‡Induction therapy, stem-cell transplantation, and maintenance were considered one line of therapy.

§One patient in cohort one initiated carfilzomib therapy but was subsequently determined to have received only one line of therapy as defined.

safety and efficacy of carfilzomib in combination with low-dose dexamethasone (40 mg weekly).

PATIENTS AND METHODS

Patients

Patients age ≥ 18 years with measurable relapsed and/or refractory MM and ≥ 2 prior lines of therapy were eligible. Other inclusion criteria included Eastern Cooperative Oncology Group performance status ≤ 2 , adequate hepatic function, absolute neutrophil count $\geq 1,000/\mu\text{L}$, platelet count $\geq 30,000/\mu\text{L}$, hemoglobin ≥ 7.0 g/dL, and creatinine clearance ≥ 20 mL/min. Therapy with approved/investigational anticancer agents or radiotherapy within 3 weeks of study initiation was not permitted. Additionally, patients were excluded if they had clinically significant cardiovascular disease (congestive heart failure New York Heart Association class III to IV, symptomatic ischemia, uncontrolled conduction abnormalities, or myocardial infarction within 3 months), active infection requiring systemic antibiotics, antivirals, or antifungals within 2 weeks, or significant neuropathy (grade 3 to 4 or grade 2 with pain per National Cancer Institute Common Terminology Criteria for Adverse Events [AEs; version 3.0]¹⁴) at study initiation.

This study was conducted according to the Declaration of Helsinki and approved by the independent ethics committee/institutional review board at each of the participating centers. Patients provided written informed consent.

Study Design and Treatment

This was a multicenter, open-label phase I study of carfilzomib administered as a 30-minute infusion. Patients were enrolled using a 3 + 3 dose-escalating design. The MTD was defined as the highest dose at which $< 33\%$ of patients experienced a treatment-related DLT during the first cycle. The MTD cohort of single-agent carfilzomib was then expanded to confirm tolerability. DLT was defined as: grade ≥ 3 nonhematologic toxicity or grade ≥ 2 neuropathy with pain, grade 4 neutropenia lasting > 7 days or febrile neutropenia, grade 4 thrombocytopenia lasting ≥ 7 days despite withholding carfilzomib, or grade ≥ 3 thrombocytopenia with bleeding. Because there was clinical experience with tolerability of the 20 mg/m² dose administered both as 2- to 10-minute and 30-minute infusions,^{9,15-18} patients who received the 20 mg/m² dose but had cytopenias or other AEs that prevented re-treatment and dose escalation were not considered in defining the MTD but were included in the safety analysis. In two additional cohorts, low-dose dexamethasone (40 mg/wk) was combined with carfilzomib 30-minute infusion at the MTD-1 and MTD levels.

Carfilzomib was administered as a 30-minute IV infusion on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Doses in cycle one days 1 and 2 were 20 mg/m², followed thereafter by dose escalation to 36, 45, 56, or 70 mg/m² in each subsequent cohort, depending on the occurrence of a DLT. Before carfilzomib infusion, dexamethasone (4 mg for carfilzomib doses ≤ 45 mg/m²; 8 mg for doses > 45 mg/m²) was administered as premedication to mitigate potential infusion-related reactions.⁹ For patients receiving carfilzomib plus dexamethasone, dexamethasone 20 mg was administered before each infusion, and 40 mg were administered on day 22 of each 28-day cycle. Patients were instructed to increase oral hydration before treatment and received pre- and postdose IV hydration with 250 to 500 mL normal saline or appropriate fluid. Antiviral prophylaxis for herpes zoster was provided. Patients receiving ≥ 12 cycles of treatment could continue on the current study or enroll onto the carfilzomib treatment-extension study (PX-171-010; NCT00884312).

Efficacy and Safety Assessments

Responses were determined according to the International Myeloma Working Group uniform response criteria,¹⁹ including minimal response (MR) per European Blood and Marrow Transplantation Group criteria²⁰ on day 15 of cycle one and day 1 of each subsequent cycle. For both single-agent and carfilzomib-plus-dexamethasone cohorts, ORR (stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR]), as well as clinical benefit rate (CBR; ORR plus MR), was evaluated throughout the study period. Additional efficacy end points included duration of response (DOR), progression-free survival (PFS), and

median time to progression (TTP). Determination of response or disease progression required two consecutive assessments. Safety assessments included AEs graded by National Cancer Institute Common Terminology Criteria for AEs (version 3.0),¹⁴ laboratory assessments, and vital signs. Physical examination and ECG were performed at baseline, during study, and within 30 days of last dose. For carfilzomib-plus-dexamethasone cohorts, baseline multiple-gated acquisition scan and pulmonary function tests were performed and repeated as indicated.

PK and PD Analyses

Blood samples for PKs were obtained at each dose level (single-agent cohorts only) on cycle one day 1 and cycle two day 16 predose, at 5 and 15 minutes after start of infusion, before end of infusion, and postinfusion at 5, 15, and 30 minutes and 1, 2, and 4 hours. A validated liquid chromatography/mass spectrometry assay was used to analyze plasma samples.⁹ Whole blood samples for PD analysis at every dose level (single-agent cohorts only) were collected predose and 1 hour after end of infusion on cycle one days 1, 2, and 8 or cycle two day 1. Proteasome CT-L activity in whole blood and peripheral blood mononuclear cells was measured as previously described.⁵

Statistical Analyses

Continuous and categorical data were summarized using descriptive statistics. Safety and efficacy populations included patients who received ≥ 1 carfilzomib dose. For the expansion and combination cohorts, DOR, TTP, and PFS were estimated using the Kaplan-Meier method; exact binomial 95% CIs were reported for each end point. Paired *t*-test analysis of proteasome inhibition (%) was performed on samples from individual patients receiving carfilzomib 20 and 56 mg/m².

RESULTS

Patient Characteristics and Disposition

This study began in August 2009 at five centers in the United States, with data cutoff in February 2013. For single-agent carfilzomib,

Table 2. Patient Disposition

Disposition	Single-Agent Carfilzomib		Carfilzomib Plus Low-Dose Dexamethasone					
	56 mg/m ² (n = 24)	Total (n = 33)	56 mg/m ² (n = 8)	Total (n = 22)				
No. of cycles								
Median	3.5	4.0	6.0	6.0				
Range	1-25	1-25	1-14	1-16				
≥ 4	12	50.0	18	54.5	6	75.0	17	77.3
Dose reduced because of AE	5	20.8	11	33.3	0	0.0	1	4.5
Entered extension study*	3	12.5	4	12.1	1	12.5	5	22.7
Discontinued drug	23	95.8	32	97.0	6	75.0	15	68.2
Progression	12	50.0	19	57.6	4	50.0	13	59.1
AE†	7	29.2	7	21.2	1	12.5	1	4.5
Other‡	4	16.7	6	18.2	1	12.5	1	4.5
Receiving active treatment	1	4.2	1	3.0	2	25.0	7	31.8

Abbreviation: AE, adverse event.

*Two patients still in extension study: one, carfilzomib 70 mg/m²; one, carfilzomib plus dexamethasone 45 mg/m².

†Single agent: acute renal failure, jaw pain, neutropenia, thrombocytopenia, thrombotic thrombocytopenic purpura, urinary tract infection, pulmonary hypertension. Carfilzomib plus dexamethasone: alanine aminotransferase increased, aspartate aminotransferase increased, generalized weakness.

‡Other includes withdrew consent, lost to follow-up, and other nonspecified.

33 patients were enrolled across four dose-escalation cohorts (four at 36, three at 45, eight at 56, and two at 70 mg/m²) and the dose expansion cohort (16 at 56 mg/m²). Median age was 65 years (Table 1). A majority of patients (66.7%) were classified as standard risk by either cytogenetics or fluorescence in situ hybridization. Patients had received a median of five (range, one to nine) prior lines of therapy, including bortezomib (90.9%) and IMiDs (93.9%). Most patients were refractory to their last regimen (84.8%), including 42.4% who were refractory to bortezomib. The carfilzomib-plus-dexamethasone cohorts enrolled 22 patients (14 at 45 and eight at 56 mg/m²).

For single-agent carfilzomib, patients received a median of 4.0 (range, one to 25) cycles (Table 2). Eleven patients overall (33.3%) and five in the 56 mg/m² group (20.8%) required dose reduction because of an AE. Thirty-two patients (97.0%) discontinued treatment, including 19 (57.6%) because of progressive disease and seven (21.2%) because of an AE. Three patients from the 56-mg/m² group and one patient from the 70-mg/m² group (reduced to 56 mg/m²) enrolled onto and received further therapy in the extension study. There was

one death within 30 days of completing treatment (not attributable to carfilzomib), and one patient continued to receive therapy (23.5 months).

In the carfilzomib-plus-dexamethasone cohorts, patients received a median of six cycles (range, one to 16); carfilzomib dose was reduced in one patient (45-mg/m² cohort). Fifteen patients (68.2%) discontinued treatment (13 because of progressive disease and one because of AE). There were no deaths within 30 days of discontinuation. Five patients (four in 45-mg/m² cohort; one in 56-mg/m² cohort) received further therapy in the extension study, and seven continued to receive therapy at data cutoff.

MTD

In the single-agent, dose-escalation portion of the study, DLTs were recorded in two patients in the 70-mg/m² cohort (grade 3 renal tubular necrosis [cycle one day 8] and grade 3 proteinuria [cycle one day 22]); after resolution of toxicity, both patients successfully continued treatment at reduced doses (one at 56 mg/m²; one at 27-45

Table 3. Treatment-Related AEs by Frequency*

AE	Single-Agent Carfilzomib								Carfilzomib Plus Low-Dose Dexamethasone							
	All Grade				Grade ≥ 3				All Grade				Grade ≥ 3			
	56 mg/m ² (n = 24)		Total (n = 33)		56 mg/m ² (n = 24)		Total (n = 33)		56 mg/m ² (n = 8)		Total (n = 22)		56 mg/m ² (n = 8)		Total (n = 22)	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Hematologic																
Thrombocytopenia	9	37.5	13	39.4	9	37.5	12	36.4	4	50.0	9	40.9	4	50.0	8	36.4
Anemia	6	25.0	9	27.3	4	16.7	5	15.2	3	37.5	6	27.3	2	25.0	4	18.2
Neutropenia	4	16.7	4	12.1	2	8.3	2	6.1	0	0.0	0	0.0	0	0.0	0	0.0
Lymphopenia	3	12.5	3	9.1	3	12.5	3	9.1	3	37.5	4	18.2	3	37.5	4	18.2
Nonhematologic																
Nausea	13	54.2	17	51.5	0	0.0	0	0.0	2	25.0	2	9.1	0	0.0	0	0.0
Dyspnea	12	50.0	13	39.4	2	8.3	2	6.1	1	12.5	4	18.2	0	0.0	0	0.0
Fatigue	11	45.8	17	51.5	1	4.2	2	6.1	2	25.0	9	40.9	0	0.0	0	0.0
Pyrexia	10	41.7	14	42.4	0	0.0	0	0.0	3	37.5	4	18.2	0	0.0	0	0.0
Chills	9	37.5	12	36.4	0	0.0	0	0.0	1	12.5	1	4.5	0	0.0	0	0.0
Vomiting	7	29.2	10	30.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Diarrhea	5	20.8	6	18.2	1	4.2	1	3.0	0	0.0	0	0.0	0	0.0	0	0.0
Headache	4	16.7	6	18.2	0	0.0	0	0.0	3	37.5	5	22.7	0	0.0	0	0.0
Cough	3	12.5	3	9.1	0	0.0	0	0.0	1	12.5	1	4.5	0	0.0	0	0.0
Dizziness	3	12.5	3	9.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Hypertension	3	12.5	4	12.1	1	4.2	2	6.1	2	25.0	5	22.7	0	0.0	2	9.1
Increased blood creatinine	3	12.5	5	15.2	0	0.0	0	0.0	0	0.0	1	4.5	0	0.0	0	0.0
Asthenia	2	8.3	2	6.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Chest pain	2	8.3	3	9.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Exertional dyspnea	2	8.3	3	9.1	0	0.0	0	0.0	0	0.0	2	9.1	0	0.0	0	0.0
Hypoxia	2	8.3	2	6.1	2	8.3	2	6.1	0	0.0	0	0.0	0	0.0	0	0.0
Increased blood creatine	2	8.3	2	6.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Insomnia	1	4.2	1	3.0	0	0.0	0	0.0	0	0.0	2	9.1	0	0.0	0	0.0
Muscle spasms	2	8.3	2	6.1	0	0.0	0	0.0	0	0.0	1	4.5	0	0.0	0	0.0
Myalgia	2	8.3	2	6.1	0	0.0	0	0.0	1	12.5	1	4.5	0	0.0	0	0.0
Pneumonia	2	8.3	2	6.1	2	8.3	2	6.1	0	0.0	1	4.5	0	0.0	1	4.5
Pulmonary hypertension	2	8.3	2	6.1	1	4.2	1	3.0	1	12.5	1	4.5	1	12.5	1	4.5
Upper respiratory tract infection	0	0.0	1	3.0	0	0.0	0	0.0	2	25.0	4	18.2	0	0.0	0	0.0
Hypokalemia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	9.1	0	0.0	0	0.0
Hypophosphatemia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	13.6	0	0.0	2	9.1
Increased blood lactate dehydrogenase	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	9.1	0	0.0	1	4.5

Abbreviation: AE, adverse event.

*In > 5% of patients receiving carfilzomib 20/56 mg/m² or in the overall cohort of patients receiving carfilzomib plus dexamethasone.

mg/m²). The 56-mg/m² cohort was expanded to six evaluable patients, one of whom had a DLT of grade 3 hypoxia with fever. Therefore, the MTD was established as 56 mg/m², and this cohort was expanded to 24 patients. To evaluate the safety of the carfilzomib-plus-dexamethasone combination, patients were started at a carfilzomib dose of 20/45 mg/m² and low-dose dexamethasone. After six patients had completed one cycle at this dose, subsequent patients were treated with 20/56 mg/m² of carfilzomib and low-dose dexamethasone; carfilzomib 20/45 mg/m² was administered to 14 patients, and 20/56 mg/m² to eight patients, without a DLT as defined for the dose-escalation portion of the study. Overenrollment onto the carfilzomib-plus-dexamethasone 45-mg/m² cohort occurred because of rapid multicenter accrual.

Safety

All 33 patients receiving single-agent carfilzomib were evaluable for safety. In the 56-mg/m² cohort (n = 24), the most common treatment-related AEs of any grade were nausea (54.2%; n = 13), dyspnea (50.0%; n = 12), fatigue (45.8%; n = 11), pyrexia (41.7%; n = 10), and thrombocytopenia and chills (both 37.5%; n = 9); a majority were grade 1 or 2. At this dose, hematologic AEs of thrombocytopenia (37.5%; n = 9) and anemia (16.7%; n = 4) were the most common treatment-related AEs of grade ≥ 3 (Table 3). Peripheral neuropathy was reported infrequently; in all four cohorts, new-onset or progressive grade 1 peripheral neuropathy was reported for two patients (6.1%), and there was one report of grade 3 peripheral sensory neuropathy in a patient with pes planus and baseline grade 2 neuropathy in the 45-mg/m² cohort. All cases were possibly related to treatment. Cardiac AEs were reported in five patients (20.8%) in the 56-mg/m² cohort. Tachycardia and cardiac failure in one patient each were possibly related to carfilzomib. Hypertension of any grade was attributed to treatment in 12.5% (n = 3) of the 56-mg/m² cohort (12.1% overall). Treatment-related and -emergent AEs were generally similar in the 56-mg/m² cohort and overall population (Table 3; Appendix Tables A1 and A2, online only).

For carfilzomib-plus-dexamethasone cohorts (Table 3), the most common treatment-related AEs overall were thrombocytopenia and fatigue (each 40.9%; n = 9), anemia (27.3%; n = 6), and hypertension and headache (each 22.7%; n = 5). Similar to single-agent carfilzomib, hematologic AEs were the most common treatment-related AEs of grade ≥ 3. At carfilzomib 56 mg/m² plus dexamethasone, nausea (25%; n = 2), fatigue (25%; n = 2), and dyspnea and chills (each 12.5%; n = 1) occurred less frequently than with carfilzomib alone. As with single-agent carfilzomib, treatment-related and -emergent AEs were similar (Appendix Tables A1 and A2, online only).

Response

For single-agent carfilzomib, ORR was 48% (95% CI, 31 to 67), with a CBR of 52% (95% CI, 34 to 69; Table 4). For the 24 patients in the 56-mg/m² cohort, ORR was 50% (95% CI, 29 to 71), including 4% (n = 1) sCR, 17% (n = 4) VGPR, and 30% (n = 7) PR. No MRs were observed. One patient with PR demonstrated > 95% decrease in free light chain from baseline and would be considered VGPR by new International Myeloma Working Group criteria for free light chain patients, as amended in 2011 (Appendix Fig A1, online only).²¹ For response-evaluable patients (n = 20) who received single-agent carfilzomib 56 mg/m², ORR was 60%

Table 4. Best Response

Response	Single-Agent Carfilzomib		Carfilzomib Plus Low-Dose Dexamethasone	
	56 mg/m ² (n = 24)	Total (n = 33)	56 mg/m ² (n = 8)	Total (n = 22)
	No.	%	No.	%
Best response				
sCR	1	4	1	3
CR	0	0	0	0
VGPR	4	17	5	15
PR	7	29	10	30
MR	0	0	1	3
SD	4	17	8	24
Progression	5	21	5	15
NE	3	13	3	9
ORR (≥ PR)				
All patients	12	50	16	48
95% CI	29-71		31-67	
Response evaluable*	12	60	16	59
95% CI	36-81		39-78	
CBR (≥ MR)				
All patients	12	50	17	52
95% CI	29-71		34-69	
Response evaluable*	12	60	17	63
95% CI	36-81		42-81	

Abbreviations: CBR, clinical benefit rate; CR, complete response; MR, minimal response; NE, not evaluable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

*Patients who completed one cycle of treatment and one postbaseline assessment.

(95% CI, 36 to 81; Table 4). Median DOR for the 56-mg/m² cohort was 8.0 months (95% CI, 5.3 to not estimable [NE]), and median TTP and PFS were 7.0 months (95% CI, 1.9 to 8.4). Median time to response was 0.5 months (95% CI, 0.5 to 1.9). For the carfilzomib-plus-dexamethasone cohorts, ORR was 55% (95% CI, 32 to 76), with a CBR of 64% (95% CI, 41 to 83; Table 4). Additionally, median PFS and TTP were 6.2 months (95% CI, 3.0 to NE), and DOR was 10.6 months (95% CI, 2.8 to NE).

PKs and PDs

Clearance of carfilzomib was rapid across all dose groups. Geometric mean area under the plasma concentration-time curve from time zero to last sampling and C_{max} exposures seemed to increase with increasing carfilzomib dose (20 to 56 mg/m²), without effect on half-life (t_{1/2}) (Table 5; Fig 1A). Because of small patient numbers and interpatient variability, dose proportionality could not be definitively established. Carfilzomib t_{1/2} was short (range, 0.837 to 1.21 hours). PD analysis showed dose-related inhibition of proteasome CT-L activity; inhibition increased from a mean of 83.1% at 20 mg/m² (range, 64.6% to 96.2%) to 97.7% at 56 mg/m² (range, 90.8% to 100%) of carfilzomib (Fig 1B). Minimal recovery of constitutive proteasome activity was observed between cycles in whole blood, whereas in peripheral blood mononuclear cells, there was recovery by the second cycle (Appendix Fig A2, online only).

Table 5. PKs of Plasma Carfilzomib on Day 16 of Cycle Two After Administration of Carfilzomib by 30-Minute Infusion

PK Parameter	20 mg/m ² (n = 31)*		27 mg/m ² (n = 1)		36 mg/m ² (n = 3)		45 mg/m ² (n = 4)		56 mg/m ² (n = 12)	
	Geometric Mean	CV (%)	Geometric Mean	CV (%)	Geometric Mean	CV (%)	Geometric Mean	CV (%)	Geometric Mean	CV (%)
AUC _{last} , ng × hr/mL	275	54.6	488	NA	702	72.4	740	24.8	948	34.0
AUC _{0-∞} , ng × hr/mL	273†	55.3	489	NA	483†	0.5	740	24.8	917†	24.4
C _{max} , ng/mL	750	65.8	1,290	NA	1,792	73.4	1,758	25.8	2,079	43.9
t _{1/2} , hours	0.837†	32.5	0.973	NA	1.21†	16.7	1.02	6.0	0.875†	30.4
CL, L/h	143†	56.6	102	NA	148†	16.7	131	27.2	118†	27.7

Abbreviations: AUC_{last}, area under plasma concentration-time curve from time zero to last sampling; AUC_{0-∞}, area under plasma concentration-time curve from time zero to infinity; CL, clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; NA, not applicable; PK, pharmacokinetic; t_{1/2}, half-life.

*Day 1 of cycle one.

†20 mg/m² (n = 28), 36 mg/m² (n = 2), 56 mg/m² (n = 10).

DISCUSSION

This study is the first to our knowledge to establish the MTD of single-agent carfilzomib administered as a 30-minute infusion in patients with relapsed and/or refractory MM. The MTD of 56 mg/m² was generally well tolerated with encouraging activity in this heavily pretreated population, a majority of whom were refractory to IMiDs and bortezomib. Additionally, single-agent carfilzomib responses were durable for the MTD cohort, with median TTP and DOR of 7.0 and 8.0 months, respectively.

The 50% ORR attained with 56 mg/m² of single-agent carfilzomib administered as a 30-minute infusion is impressive, particularly considering the 23.7% ORR reported for single-agent carfilzomib at 27 mg/m² in a similar patient population.⁸ Although direct comparison with other trials should be made with caution, the ORR reported herein compares favorably to single-agent responses with bortezomib (38%),^{22,23} lenalidomide (26%),²⁴ and pomalidomide (13%)²⁵ in patients with relapsed and/or refractory MM. Similarly, the ORR for single-agent carfilzomib and carfilzomib plus dexamethasone compares favorably to that reported for high-dose dexametha-

sone with lenalidomide^{26,27} and low-dose dexamethasone with pomalidomide (32%)²⁸ in patients with relapsed and/or refractory MM.

The overall safety profile reported here for a 30-minute infusion of single-agent carfilzomib 56 mg/m² is consistent with that seen in previous phase II studies of single-agent carfilzomib 20/27 mg/m² administered over 2 to 10 minutes.^{8,17,29} Additionally, no new or unexpected AEs were observed. At 56 mg/m², although the incidence of certain all-grade, treatment-related, constitutional AEs, including nausea (54.2% v 34%), dyspnea (50.0% v 17%), and pyrexia (41.7% v 15%), was higher than that observed in studies of carfilzomib 27 mg/m² administered over 2 to 10 minutes,⁸ the AEs were typically low grade. Despite the higher carfilzomib dose, peripheral neuropathy was only reported in 9.1% of patients treated with single-agent carfilzomib, including one patient in the 56-mg/m² cohort.

The incidence of cardiac failure (4.2%) with single-agent carfilzomib was similar to that previously observed at 27 mg/m² (3.8%)⁸; however, these results require confirmation in larger trials. At the 27-mg/m² dose, no discernible characteristics that predispose patients to cardiopulmonary toxicities have been identified.^{8,30} Data on cardiopulmonary toxicity with

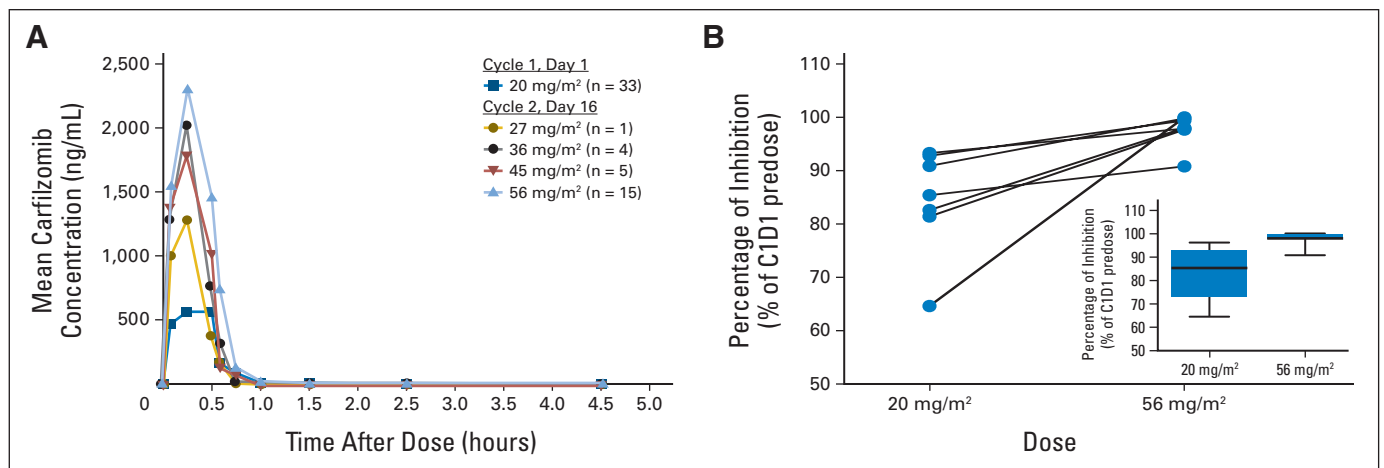


Fig 1. (A) Pharmacokinetics of plasma carfilzomib on day 1 of cycle one (C1D1) and day 16 of cycle two after administration of carfilzomib by 30-minute infusion. (B) Pharmacodynamics of carfilzomib administered by 30-minute infusion. Boxplot representation of percentage of proteasome inhibition at 20 and 56 mg/m² (inset plot). Peripheral blood mononuclear cell samples collected before and 1 hour after dosing on day 1 of cycle one (20 mg/m²; n = 11) and two (56 mg/m²; n = 7). Values were normalized to C1D1 predose. Line plot illustrates paired samples for seven patients receiving carfilzomib at 20 and 56 mg/m². Each line represents individual patient (paired *t* test *P* = .02).

30-minute infusion at 56 mg/m² are limited. A phase II study of 30-minute infusion of carfilzomib at 56 mg/m² in 41 patients with relapsed and/or refractory MM reported preliminary data of grade \geq 3 pulmonary edema/cardiac failure in 10% and hypertension in 20% of patients, 50% of whom required dose reduction.³¹ The fact that 24% of patients in this study had undergone allogeneic transplantation may have adversely affected the grade and incidence of cardiopulmonary toxicity.³² The pathogenesis of dyspnea in patients treated with carfilzomib remains speculative. The emphasis on vigorous pre- and post-therapy hydration in our study and the higher doses of carfilzomib may have contributed to the observed increased incidence of dyspnea and hypertension. Until more definitive cardiopulmonary toxicity data become available, it would be clinically prudent to consider the 56-mg/m² dosing schedule cautiously. Ongoing phase III randomized trials of 30-minute infusion aim to address both the pertinent questions of predisposing factors and prevalence of cardiopulmonary toxicity associated with carfilzomib.

Safety and efficacy results of the carfilzomib-plus-dexamethasone cohorts should be interpreted with caution because of the small number of enrolled patients. The combination of carfilzomib plus dexamethasone was well tolerated, except for more frequent headache, hypertension, and upper respiratory tract infection; there were no new treatment-related AEs. Less frequent nausea, dyspnea, chills, fatigue, vomiting, and diarrhea relative to respective doses of single-agent carfilzomib were noted, as might be anticipated with the addition of low-dose dexamethasone and as reported previously with bortezomib.¹

Carfilzomib showed rapid systemic clearance and short $t_{1/2}$ after a 30-minute infusion at doses of 20 to 56 mg/m², concordant with those observed previously with 2- to 10-minute infusions.¹² Exposure to carfilzomib in general increased with dose. Consistent with the preclinical in vivo PK data,¹² 30-minute carfilzomib infusion resulted in an approximately three-fold lower C_{max} and similar area under the curve relative to 2- to 10-minute infusions at 36 mg/m². The systemic clearance, terminal $t_{1/2}$, and constitutive proteasome inhibition were comparable.³³ Our study demonstrates dose-dependent inhibition of the CT-L active site of the c20S (β 5) constitutive proteasome. Preliminary exploratory PD studies have also shown dose-dependent inhibition of all three i20s (LMP7, MECL1, LMP2) immunoproteasome subunits.³⁴ Because myeloma cells are characterized by a predominance of immunoproteasomes compared with constitutive proteasomes, the increase in immunoproteasome inhibition associated with increasing carfilzomib doses may partly account for the improved clinical response.³⁴

In summary, carfilzomib administered as a 30-minute infusion at 56 mg/m², as a single agent or in combination with low-dose dexamethasone 40 mg per week, was generally well tolerated and highly active in patients with relapsed and/or refractory MM. These data and this dosing schema

have provided the basis for a phase III randomized, multicenter trial (ENDEAVOR [Randomized, Open-Label, Phase III Study of Carfilzomib Plus Dexamethasone Versus Bortezomib Plus Dexamethasone in Patients With Relapsed Multiple Myeloma]; NCT01568866) that is currently comparing a 30-minute infusion of carfilzomib 56 mg/m² plus low-dose dexamethasone versus bortezomib plus low-dose dexamethasone in patients with relapsed MM.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Naseem Zojwalla, Onyx Pharmaceuticals (C); Susan Lee, Onyx Pharmaceuticals (C); Zhengping Wang, Onyx Pharmaceuticals (C) **Consultant or Advisory Role:** Kyriakos P. Papadopoulos, Proteolix/Onyx Pharmaceuticals (C); David H. Vesole, Onyx Pharmaceuticals (C); Steven T. Rosen, Non-Hodgkin Lymphoma/Chronic Lymphocytic Leukemia Think Tank TGM (C) **Stock Ownership:** Naseem Zojwalla, Onyx Pharmaceuticals; Susan Lee, Onyx Pharmaceuticals; Zhengping Wang, Onyx Pharmaceuticals **Honoraria:** David S. Siegel, Onyx Pharmaceuticals; David H. Vesole, Onyx Pharmaceuticals; Steven T. Rosen, Non-Hodgkin Lymphoma/Chronic Lymphocytic Leukemia Think Tank TGM **Research Funding:** Kyriakos P. Papadopoulos, Proteolix/Onyx Pharmaceuticals **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

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Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

- Jagannath S, Richardson PG, Barlogie B, et al: Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. *Haematologica* 91: 929-934, 2006
- Lonial S, Mitsiades CS, Richardson PG: Treatment options for relapsed and refractory multiple myeloma. *Clin Cancer Res* 17:1264-1277, 2011
- Laubach JP, Mitsiades CS, Mahindra A, et al: Management of relapsed and relapsed/refractory multiple myeloma. *J Natl Compr Canc Netw* 9:1209-1216, 2011
- Kumar SK, Lee JH, Lahuerta JJ, et al: Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter International Myeloma Working Group study. *Leukemia* 26:149-157, 2012
- Demo SD, Kirk CJ, Aujay MA, et al: Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. *Cancer Res* 67:6383-6391, 2007
- Kuhn DJ, Chen Q, Voorhees PM, et al: Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. *Blood* 110: 3281-3290, 2007
- Kyprolis prescribing information. Onyx Pharmaceuticals, South San Francisco, CA, 2012
- Siegel DS, Martin T, Wang M, et al: A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* 120:2817-2825, 2012

9. Alsina M, Trudel S, Furman RR, et al: A phase I single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed or refractory multiple myeloma or lymphoma. *Clin Cancer Res* 18:4830-4840, 2012
10. Squifflet P, Michiels S, Siegel D, et al: Multivariate modelling reveals evidence of a dose-response relationship in phase 2 studies of single-agent carfilzomib. *Blood* 118, 2011 (abstr 1877)
11. Hawley TS, Riz I, Yang W, et al: Identification of an ABCB1 (P-glycoprotein)-positive carfilzomib-resistant myeloma subpopulation by the pluripotent stem cell fluorescent dye CDy1. *Am J Hematol* 88:265-272, 2013
12. Yang J, Wang Z, Fang Y, et al: Pharmacokinetics, pharmacodynamics, metabolism, distribution, and excretion of carfilzomib in rats. *Drug Metab Dispos* 39:1873-1882, 2011
13. Jiang J, Kirk C, Muchamuel T, et al: The benefits of irreversibility: Infusion administration of carfilzomib results in potent proteasome inhibition and improved safety in animals. *Cancer Res* 71, 2011 (abstr 2607)
14. Common Terminology Criteria for Adverse Events, version 3.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf
15. Papadopoulos KP, Burris HA 3rd, Gordon M, et al: A phase I/II study of carfilzomib 2-10-min infusion in patients with advanced solid tumors. *Cancer Chemother Pharmacol* 72:861-868, 2013
16. Jakubowiak AJ, Dytfeld D, Griffith KA, et al: A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood* 120:1801-1809, 2012
17. Vij R, Wang M, Kaufman JL, et al: An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. *Blood* 119:5661-5670, 2012
18. Jagannath S, Vij R, Stewart AK, et al: An open-label single-arm pilot phase II study (PX-171-003-A0) of low-dose, single-agent carfilzomib in patients with relapsed and refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk* 12:310-318, 2012
19. Durie BG, Harousseau JL, Miguel JS, et al: International uniform response criteria for multiple myeloma. *Leukemia* 20:1467-1473, 2006
20. Bladé J, Samson D, Reece D, et al: Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation: Myeloma Subcommittee of the EBMT—European Group for Blood and Marrow Transplant. *Br J Haematol* 102:1115-1123, 1998
21. Rajkumar SV, Harousseau JL, Durie B, et al: Consensus recommendations for the uniform reporting of clinical trials: Report of the International Myeloma Workshop Consensus Panel 1. *Blood* 117:4691-4695, 2011
22. Richardson PG, Sonneveld P, Schuster MW, et al: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 352:2487-2498, 2005
23. Moreau P, Richardson PG, Cavo M, et al: Proteasome inhibitors in multiple myeloma: 10 years later. *Blood* 120:947-959, 2012
24. Richardson P, Jagannath S, Hussein M, et al: Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. *Blood* 114:772-778, 2009
25. Richardson PG, Siegel D, Baz R, et al: Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib. *Blood* 121:1961-1967, 2013
26. Weber DM, Chen C, Niesvizky R, et al: Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 357:2133-2142, 2007
27. Dimopoulos M, Spencer A, Attal M, et al: Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 357:2123-2132, 2007
28. Lacy MQ, Hayman SR, Gertz MA, et al: Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). *Leukemia* 24:1934-1939, 2010
29. Vij R, Siegel DS, Jagannath S, et al: An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib. *Br J Haematol* 158:739-748, 2012
30. Siegel D, Martin T, Nooka A, et al: Integrated safety profile of single-agent carfilzomib: Experience from 526 patients enrolled in 4 phase II clinical studies. *Haematologica* 98:1753-1761, 2013
31. Lendvai N, Landau H, Lesokhin A, et al: Phase II study of infusional carfilzomib in patients with relapsed or refractory multiple myeloma. *Blood* 120, 2012 (abstr 947)
32. Armenian SH, Sun CL, Vase T, et al: Cardiovascular risk factors in hematopoietic cell transplantation survivors: Role in development of subsequent cardiovascular disease. *Blood* 120:4505-4512, 2012
33. Papadopoulos K, Lee P, Singhal S, et al: PPX-171-007: A phase 1b study evaluating the safety and efficacy of a 30-minute IV infusion of carfilzomib in patients with relapsed and/or refractory (R/R) multiple myeloma (MM). *Haematologica* 96, 2011 (abstr 0898)
34. Lee S, Arastu-Kapur S, Kellerman L, et al: Potent inhibition of selective proteasome subunits by carfilzomib in multiple myeloma and solid tumor patients is associated with patients response. *Haematologica* 97, 2012 (abstr 0840)

Acknowledgment

We thank all of the patients and their families who contributed to this study, the staff from the participating study sites, and all of the participating research nurses and data coordinators, as well as Ju Rueyjiuan Lee (Onyx Pharmaceuticals) for statistical support, Leanne M. McCulloch, PharmD (Onyx Pharmaceuticals) for safety analysis support, Thomas Renau, PhD (Onyx Pharmaceuticals) for critical review of the manuscript, and Melissa Kirk, PhD (Fishawack Communications) for medical writing and editorial assistance.

Appendix**Table A1.** Treatment-Emergent AEs by Frequency*

AE	Single-Agent Carfilzomib										Carfilzomib Plus Low-Dose Dexamethasone					
	20/36 mg/m ² (n = 4)		20/45 mg/m ² (n = 3)		20/56 mg/m ² (n = 24)		20/70 mg/m ² (n = 2)		Total (n = 33)		20/45 mg/m ² (n = 14)		20/56 mg/m ² (n = 8)		Total (n = 22)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematologic																
Thrombocytopenia	1	25.0	1	33.3	10	41.7	2	100.0	14	42.4	5	35.7	4	50.0	9	40.9
Anemia	2	50.0	1	33.3	9	37.5	1	50.0	13	39.4	5	35.7	3	37.5	8	36.4
Lymphopenia	0	0.0	0	0.0	3	12.5	0	0.0	3	9.1	2	14.3	3	37.5	5	22.7
Nonhematologic																
Fatigue	3	75.0	3	100.0	14	58.3	2	100.0	22	66.7	8	57.1	5	62.5	13	59.1
Pyrexia	2	50.0	1	33.3	14	58.3	1	50.0	18	54.5	2	14.3	3	37.5	5	22.7
Dyspnea	1	25.0	0	0.0	13	54.2	0	0.0	14	42.4	5	35.7	2	25.0	7	31.8
Nausea	3	75.0	2	66.7	13	54.2	1	50.0	19	57.6	4	28.6	3	37.5	7	31.8
Hypertension	2	50.0	1	33.3	10	41.7	1	50.0	14	42.4	5	35.7	2	25.0	7	31.8
Chills	1	25.0	2	66.7	9	37.5	0	0.0	12	36.4	0	0.0	1	12.5	1	4.5
Headache	1	25.0	1	33.3	8	33.3	1	50.0	11	33.3	5	35.7	3	37.5	8	36.4
Vomiting	2	50.0	1	33.3	8	33.3	1	50.0	12	36.4	3	21.4	0	0.0	3	13.6
Dizziness	0	0.0	0	0.0	7	29.2	0	0.0	7	21.2	3	21.4	1	12.5	4	18.2
Cough	1	25.0	1	33.3	7	29.2	1	50.0	10	30.3	7	50.0	2	25.0	9	40.9
Insomnia	0	0.0	1	33.3	7	29.2	0	0.0	8	24.2	5	35.7	2	25.0	7	31.8
Diarrhea	0	0.0	1	33.3	6	25.0	1	50.0	8	24.2	1	7.1	3	37.5	4	18.2
Chest pain	1	25.0	0	0.0	5	20.8	0	0.0	6	18.2	1	7.1	0	0.0	1	4.5
Peripheral edema	2	50.0	1	33.3	5	20.8	0	0.0	8	24.2	2	14.3	1	12.5	3	13.6
Upper respiratory tract infection	1	25.0	0	0.0	5	20.8	1	50.0	7	21.2	6	42.9	4	50.0	10	45.5
Back pain	1	25.0	0	0.0	4	16.7	0	0.0	5	15.2	4	28.6	2	25.0	6	27.3
Hypokalemia	1	25.0	0	0.0	1	4.2	0	0.0	2	6.1	5	35.7	0	0.0	5	22.7

Abbreviation: AE, adverse event.

*In > 20% of patients receiving carfilzomib 20/56 mg/m² or any patient receiving carfilzomib plus dexamethasone.

30-Minute Infusion of Single-Agent Carfilzomib

Table A2. Grade \geq 3 Treatment-Emergent AEs by Frequency*

AE	Single-Agent Carfilzomib										Carfilzomib Plus Low-Dose Dexamethasone					
	20/36 mg/m ² (n = 4)		20/45 mg/m ² (n = 3)		20/56 mg/m ² (n = 24)		20/70 mg/m ² (n = 2)		Total (n = 33)		20/45 mg/m ² (n = 14)		20/56 mg/m ² (n = 8)		Total (n = 22)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematologic																
Thrombocytopenia	0	0.0	1	33.3	10	41.7	2	100.0	13	39.4	4	28.6	4	50.0	8	36.4
Anemia	0	0.0	1	33.3	6	25.0	1	50.0	8	24.2	4	28.6	2	25.0	6	27.3
Neutropenia	0	0.0	0	0.0	2	8.3	0	0.0	2	6.1	0	0.0	0	0.0	0	0.0
Lymphopenia	0	0.0	0	0.0	3	12.5	0	0.0	3	9.1	2	14.3	3	37.5	5	22.7
Nonhematologic																
Hypertension	0	0.0	0	0.0	3	12.5	1	50.0	4	12.1	3	21.4	0	0.0	3	13.6
Pneumonia	0	0.0	0	0.0	3	12.5	0	0.0	3	9.1	1	7.1	1	12.5	2	9.1
Dyspnea	0	0.0	0	0.0	2	8.3	0	0.0	2	6.1	1	7.1	0	0.0	1	4.5
Fatigue	0	0.0	0	0.0	2	8.3	1	50.0	3	9.1	0	0.0	0	0.0	0	0.0
Hypoxia	0	0.0	0	0.0	2	8.3	0	0.0	2	6.1	0	0.0	0	0.0	0	0.0
Hypophosphatemia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	14.3	0	0.0	2	9.1

Abbreviation: AE, adverse event.

*In > 5% of patients receiving carfilzomib 20/56 mg/m² or any patient receiving carfilzomib plus dexamethasone.

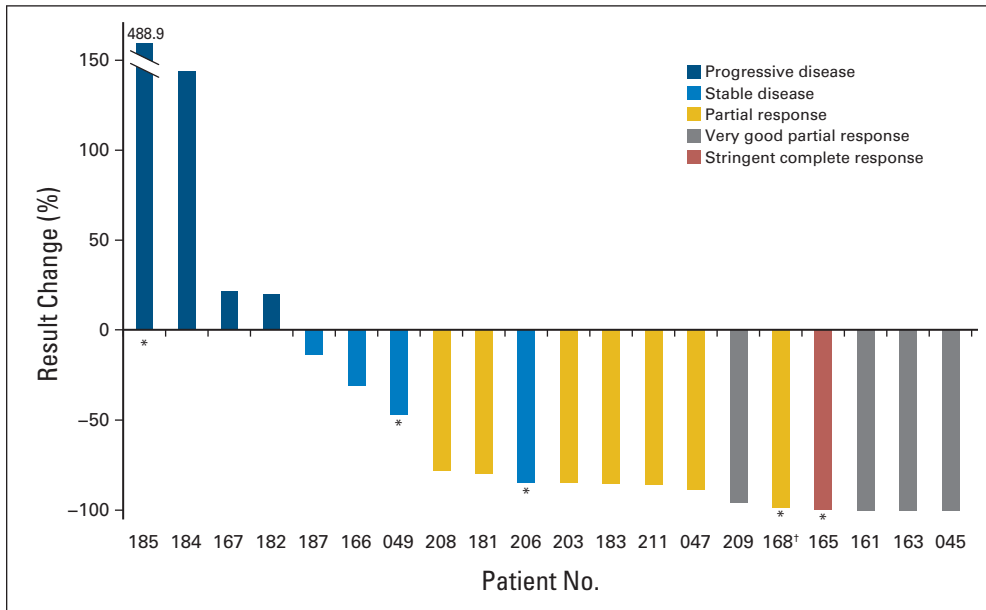


Fig A1. Waterfall plot of response data for 20/56-mg/m² cohort. (*) Response by serum free light chain only; others by serum protein electrophoresis or urine protein electrophoresis. (†) Response for patient 168 would be very good partial response under new International Myeloma Working Group guidelines.²¹

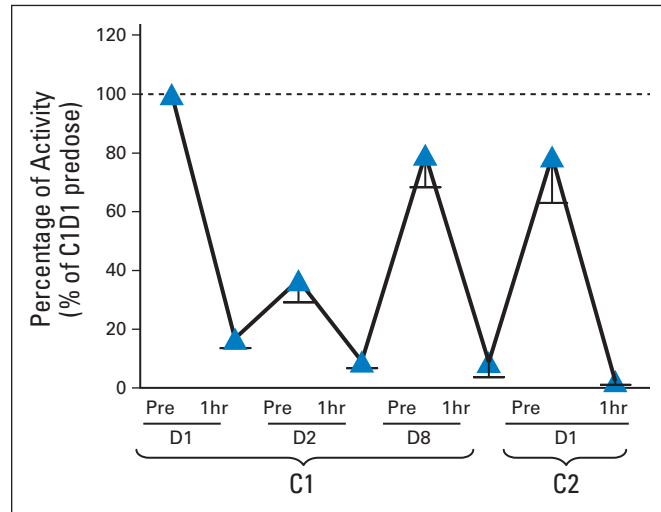


Fig A2. Time course of CT-L activity inhibition at 20/56 mg/m². Peripheral blood mononuclear cell samples collected before and 1 hour after dosing. Number of patients seven to 11 (depending on time points). Values normalized to cycle one day 1 (C1D1) predose.