Title: A phase 1 single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed or refractory multiple myeloma or lymphoma

Authors: Melissa Alsina,[1] Suzanne Trudel,[2] Richard R. Furman,[3] Peter J. Rosen,[4] Owen A. O'Connor,[5] Raymond L. Comenzo,[6] Alvin Wong,[7] Lori A. Kunkel,[8] Christopher J. Molineaux,[9] and Andre Goy[10]

Affiliations: [1]H. Lee Moffitt Cancer and Research Center, Tampa, FL, USA; [2]University of Toronto Princess Margaret Hospital, Toronto, ON, Canada; [3]Weill Cornell Medical College, New York, NY, USA; [4]Tower Cancer Research Foundation, Beverly Hills, CA, USA;[5] NYU Clinical Cancer Center, New York, NY, USA; [6]Tufts University, Boston, MA, USA; [7]Onyx Pharmaceuticals, South San Francisco, CA, USA; [8]Independent Consultant, San Francisco, CA, USA; [9]CJM Consulting, San Francisco, CA, USA; [10]John Theurer Cancer Center, Hackensack, NJ, USA

Running Head: Phase 1 carfilzomib safety and antitumor activity

Statement of Prior Presentation: Presented in abstract form at the 49th Annual Meeting of the American Society of Hematology, 2007.

Keywords: proteasome inhibitor, relapsed and/or refractory multiple myeloma, non-Hodgkins lymphoma, Waldenström macroglobulinemia, Hodgkins disease

Financial Support: Funding for this study and manuscript were provided by Onyx Pharmaceuticals.

Correspondence: Melissa Alsina, H. Lee Moffitt Cancer and Research Center, The University of South Florida, 12902 Magnolia Drive, Tampa, FL 33612, USA; e-mail: melissa.alsina@moffitt.org.

Disclosure of Conflicts of Interest:

Melissa Alsina: Advisory Board for Millennium; Research Support from Millennium, Ortho Biotech, and Celgene
Suzanne Trudel: No conflicts to disclose
Richard R. Furman: No conflicts to disclose
Peter J. Rosen: No conflicts to disclose
Owen A. O'Connor: Scientific Advisory Board for Onyx Pharmaceuticals
Raymond L. Comenzo: Consultant and serves on scientific advisory committees for Millenium and Neotope
Alvin Wong: Employment with Onyx Pharmaceuticals
Lori A. Kunkel: Stock ownership in Proteolix
Christopher J. Molineaux: Stock ownership in Proteolix and Consultant for Onyx Pharmaceuticals
Andre Goy: Consultant for Millennium, Celgene, and Onyx

Word Counts:
Text (*inclusive of Introduction through Discussion): 3,992*
Abstract: 253

Figure/Table Count:
Figures: 1; Tables: 6

Reference Count: 27

Statement of Translational Relevance

The activity of the reversible proteasome inhibitor (PI) bortezomib in preclinical and clinical studies validated the proteasome as a therapeutic target in patients with a subset of hematologic malignancies including multiple myeloma (MM). While subsequent incorporation of bortezomib into the treatment paradigm for MM has had a favorable impact on the course of disease, resistance emerges in a significant proportion of patients, and painful peripheral neuropathy can severely limit treatment. Carfilzomib is a next-generation, irreversible PI with increased selectivity for the proteasome's chymotrypsin-like active site. This second phase 1 study shows that carfilzomib is active and well tolerated on a dosing schedule of 2 consecutive days for 3 of 4 weeks in patients with relapsed and refractory hematologic malignancies, particularly MM. These data support the further development of carfilzomib and provide the basis for the dosing schedule used in ongoing phase 2 and 3 clinical evaluation in MM and other malignancies.

Abstract ***(Word count: 253)***

Introduction: Carfilzomib is a next-generation, selective, proteasome inhibitor with clinical activity in relapsed and/or refractory multiple myeloma (MM). The objectives of this phase 1 study were to establish the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles of escalating doses of carfilzomib in patients with relapsed or refractory hematologic malignancies.

Methods: Carfilzomib (doses ranging from 1.2–27 mg/m^2) was administered intravenously on 2 consecutive days for 3 weeks of a 4-week cycle. Single-agent dose escalation (n=37) was followed by a dose-expansion phase (n=11) that comprised 2 cohorts (carfilzomib or carfilzomib + dexamethasone). During dose expansion, carfilzomib was administered starting with 20 mg/m^2 during the first week (Days 1, 2) and then escalated to 27 mg/m^2 thereafter.

Results: A maximum tolerated dose (MTD) was not reached during dose escalation. Dosing in the expansion cohort was well tolerated. Adverse events (AEs) were manageable and primarily of Grade 1 or 2. The main hematologic AEs ≥ Grade 3 were anemia and thrombocytopenia. Notably, there were no observations of ≥ Grade 3 peripheral neuropathy. Carfilzomib was cleared rapidly with an elimination half-life of <30 min but still induced dose-dependent inhibition of the 20S chymotrypsin-like proteasome activity. At doses of 15–27 mg/m^2, there was evidence of activity among patients with MM and with non-Hodgkin lymphoma.

Conclusions: Escalated dosing of carfilzomib on a schedule of 2 consecutive days for 3 weeks of a 4-week cycle was tolerable and showed promising activity. This dose regimen has been selected for ongoing and future clinical studies, including PX-171-003A1 and the pivotal trial ASPIRE.

Introduction

The 20S proteasome is a central regulator of cellular homeostasis through its function in ubiquitin-dependent turnover of proteins regulating signal transduction, cell-cycle progression, apoptosis, survival, and stress response pathways. Cancer cells appear to be particularly dependent upon these proteasome-regulated pathways (1-4). The 3 proteolytic activities of the 20S proteasome core include chymotrypsin-like, trypsin-like, and caspase-like activities (5). The chymotrypsin-like activity is critical to cell survival and is a target of the clinically available proteasome inhibitors (PIs) (6). The proteasome was initially validated as a therapeutic target in multiple myeloma (MM) (7, 8) with the US approval of bortezomib (Velcade®, Millennium Pharmaceuticals, Cambridge, MA).

Carfilzomib (formerly PR-171; Onyx Pharmaceuticals, South San Francisco, CA) is a next-generation PI that is structurally and mechanistically distinct from boronate-based PIs such as bortezomib (9-11). Although both target the proteasome's chymotrypsin-like activity, their mechanisms of action and selectivity differ due to their pharmacophores and peptide sequences (6). Carfilzomib exhibits a high degree of specificity for the catalytic *N*-terminal threonine residues in each of the proteolytic active sites within the proteasome (9, 10). The peptide portion of carfilzomib confers a high degree of selectivity for chymotrypsin-like activity over the other 2 active sites of the proteasome (9). In contrast, boronate PIs such as bortezomib, originally developed as potent serine protease inhibitors, retain some cross-reactivity against other proteases (11, 12).

Another important distinction between carfilzomib and bortezomib is the stability of carfilzomib's interaction with the proteasome. Bortezomib is a slowly reversible inhibitor of the

proteasome, and recovery from inhibition results from a combination of the off-rate from the enzyme and *de novo* synthesis of new proteasomes. In contrast, proteasome inhibition by carfilzomib is mechanistically irreversible (9, 10) as it involves the formation of 2 covalent bonds; new protein synthesis is therefore required for recovery of cellular proteasome activity. Consequently, proteasome inhibition with carfilzomib is sustained over a longer period of time than with bortezomib (9).

Mechanistic differences between carfilzomib and bortezomib may account for observed differences in pre-clinical antitumor and tolerability studies. *In vitro*, carfilzomib demonstrated greater antitumor activity compared to bortezomib and overcame resistance to bortezomib and other conventional agents (13). Moreover, studies showed that carfilzomib could potentially be administered clinically on consecutive days, thereby producing significant proteasome inhibition over extended periods of time, whereas bortezomib cannot (7).

In human tumor xenograft studies, potent antitumor activity was seen when carfilzomib was administered on a weekly schedule of Day (D) 1/D2 (9). Notably, the antitumor efficacy of carfilzomib delivered on 2 consecutive days was greater than that of bortezomib administered on its clinical dosing schedule (biweekly, D1/D4) in the same models. Re-administration of carfilzomib prior to full recovery of proteasome activity resulted in optimal antitumor activity, supporting the hypothesis that prolonged proteasome inhibition (i.e., >48 hours) enhances antitumor activity *in vivo.*

Collectively, these findings led to the design of 2 separate phase 1 studies. In the first study (PX-171-001), carfilzomib was administered to patients with relapsed or refractory hematologic malignancies on a 2-week cycle, with doses up to 20 mg/m^2 given daily for 5 consecutive days,

followed by 9 days of rest (14). A dose of 15 mg/m^2 was established as the maximum tolerated dose (MTD) on this schedule and produced promising preliminary responses in patients with MM and Waldenström's macroglobulinemia (WM) (14).

In the present study (PX-171-002), carfilzomib was administered in a 4-week cycle (D1/2, D8/9, D15/16, followed by 12 days of rest). It was hypothesized that this regimen could display improved tolerability while still providing prolonged proteasome inhibition and disease control in patients with advanced hematologic malignancies. The safety, tolerability, and PK/PD profile from this study are presented herein.

Patients and Methods

Human patient protection and clinical trial registration

The protocol, informed consent, and other relevant study documentation were approved by the appropriate Institutional Review Boards prior to patient enrollment. All participants provided written informed consent in accordance with federal and local institutional guidelines. This trial was registered at www.clinicaltrials.gov as NCT00150462.

Eligibility criteria

Patients ≥18 years of age with histologically confirmed MM, non-Hodgkin lymphoma (NHL), WM, or Hodgkin lymphoma (HL) and treatment-refractory or relapsed disease after ≥2 prior therapies were eligible for the study. Other key eligibility criteria included: Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2; expected survival >6 weeks; no radiation, chemotherapy, or immunotherapy <4 weeks prior to study screening; and no active infections. Baseline white blood cell counts must have been ≥2 x 10^9/L, absolute neutrophil count (ANC) ≥1 x 10^9/L, hemoglobin level ≥8 g/dL, and platelet count ≥ 50 x 10^9/L. Patients with prior bortezomib treatment were eligible, as were patients with a history of peripheral neuropathy (PN), provided the neuropathy was < Grade 2 at study entry. Other eligibility criteria included adequate cardiovascular, hepatic, and renal function (CrCL ≥30 mL/min).

Objectives

This study consisted of sequential dose-escalation and dose-expansion phases. The primary objectives of the study were to establish the safety, tolerability, and pharmacokinetic (PK) profile of escalating doses of carfilzomib, in patients with relapsed or refractory hematologic malignancies. This included the determination of dose-limiting toxicity, identification of the MTD, and evaluating safety and tolerability at the recommended phase 2 dose with and without dexamethasone. Secondary objectives included determination of the pharmacodynamic (PDn) profiles of escalating doses of carfilzomib and evaluation of preliminary evidence of antitumor activity.

Study design

Carfilzomib was provided as a sterile, frozen liquid formulation containing 2 mg/mL of carfilzomib (Onyx Pharmaceuticals, Inc, South San Francisco, CA, USA). Patients were enrolled in cohorts of 3–6 individuals to receive carfilzomib in a dose-escalating fashion to establish the MTD. Planned dose levels ranged from 1.2–27 mg/m^2. The initial carfilzomib dose level (1.2 mg/m^2) was one-tenth of the severely toxic dose in 10% of animals based on data from rodent studies (Onyx Pharmaceuticals, Inc., data on file). Carfilzomib was given as a 1- to 2-minute IV infusion on D1/2, D8/9, D15/16 in each 28-day cycle (C). Dose escalation occurred according to a modified 3+3 Fibonacci schema. For dose escalation, 3 assessable patients had to complete their first cycle without dose-limiting toxicities (DLTs) (Table 1). When 1 DLT was seen, an additional 3 assessable patients were accrued, and further escalation could occur if no additional DLTs were seen.

Patients continued to receive carfilzomib for up to 12 cycles or until disease progression or unacceptable toxicity per investigator assessment. Intra-patient dose escalation was permitted

during the dose-escalation phase only after the intended dose was shown to be safe in the corresponding cohort.

The dose-expansion phase included a single-agent carfilzomib cohort and a carfilzomib + dexamethasone cohort. Patients received carfilzomib at 20 mg/m^2 on D1 and D2 of C1 and were dose-escalated to 27 mg/m^2 thereafter. Based on early observations in this study, as well as preclinical data and other carfilzomib trials including PX-171-001 and PX-171-003-A0, that carfilzomib administration may be associated with a first-dose infusion reaction, variably characterized by a constellation of symptoms including fevers, chills, and/or dyspnea (14, 15), some patients in the single-agent carfilzomib cohort received prophylactic dexamethasone (4 mg) in C1 and at the first dose-escalation cycle to mitigate potential symptoms. Patients with MM in the single-agent carfilzomib expansion cohort who failed to achieve a partial response (PR) or better by C2 or a complete response (CR) by C4 could initiate treatment with dexamethasone 20 mg orally (120 mg/cycle) before each carfilzomib dose. Patients in the carfilzomib + dexamethasone cohort received 20 mg oral dexamethasone prior to each dose of carfilzomib but did not receive the prophylactic 4-mg dose.

Safety criteria

Patients who received at least 1 dose of PR-171 were evaluated for safety. Safety and tolerability were evaluated by means of drug-related DLT, AE reports, physical examinations, and laboratory safety evaluations.

Response criteria

All patients who received 1 cycle of treatment and who had both baseline and at least 1 post-treatment disease assessment were considered evaluable for response. Response was based on criteria defined by the European Group for Blood and Marrow Transplantation (EBMT) for patients with MM,(16) the International Working Group for patients with NHL and HL,(17) and the Consensus Panel Recommendations from the Second International Workshop on Waldenström's Macroglobulinemia for patients with WM(18).

Pharmacokinetics

Blood samples for PK analysis were collected on C1D1, C1D2, and C1D8, and on C2D1 immediately before carfilzomib dosing and at 5, 15, 30, 60, 120, and 240 minutes after dosing. Plasma samples for PK studies were assayed using validated liquid chromatography/mass spectrometry, with a lower limit of detection of 0.10 μg/mL.

Pharmacodynamics

A PDn assay measuring inhibition of proteasome chymotrypsin-like activity in whole blood and peripheral blood mononuclear cells (PBMCs) was utilized(9). Blood samples for PDn assays were collected pre-dose and 1 hour post-dose on C1D1, C1D2, C1D8, and C2D1. Proteasome activity in all samples was compared with the C1D1 pre-dose baseline value.

Data analysis

Adverse events (AEs) were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (19). PK data were analyzed and modeled using WinNonLin Professional software, Version 5.2 (Pharsight Corp, Mountain View, CA, USA).

Results

Demographics

Forty-eight patients with relapsed or refractory hematologic malignancies were enrolled at 5 participating centers in the United States between September 2005 and April 2007. The dose-escalation phase enrolled 37 patients (21 MM, 15 NHL, 1 HL). The median age of enrolled patients was 61.4 years (range: 25–82 years) and the median time from diagnosis was 3.9 years (range: 0.7–13.7 years) (Table 2). Eleven patients (7 MM, 2 WM, 2 NHL) were treated in the dose-expansion phase, including 7 in the single-agent carfilzomib cohort and 4 in the carfilzomib + dexamethasone cohort. The median age for these patients was 65.0 years (range: 38–77 years) and the median time from diagnosis was 7.0 years (range: 3.1–22.9 years) (Table 1).

Dosing

In the dose-escalation phase of the study carfilzomib doses ranged from 1.2–27 mg/m^2 (Table 3A). Patients completed a mean of 3.9 cycles (range: 0–14 cycles). Five patients had their starting carfilzomib dose escalated: 1 each at 2.4, 4, 6, 8.4, and 15 mg/m^2; the safety, PK, and biological responses for these patients are reported according to their starting carfilzomib dose levels.

In the dose-expansion phase, all 11 patients initiated carfilzomib at a dose of 20 mg/m^2 (Table 3B). Five of 7 patients in the single-agent carfilzomib cohort escalated to 27 mg/m^2: 3 in C1 and 2 in C2.Two patients discontinued treatment in C1. Of 4 patients in the carfilzomib + dexamethasone cohort, 1 escalated to 27 mg/m^2 in C1, 2 escalated to 27 mg/m^2 in C2, and 1 discontinued treatment in C1. Patients completed a mean of 3.9–4.0 cycles (range: 1–12).

Safety results

AEs were reported in all patients during the dose-escalation and the dose-expansion phases. Most AEs were Grade 1/2 in severity in both phases, with the exceptions of anemia and thrombocytopenia, a majority of which were ≥ Grade 3 AEs (Table 4; Supplemental Table 1). Two patients discontinued due to drug-related AEs in the dose-escalation portion of the study. No patients discontinued the study during dose expansion due to drug-related AEs. Two patients had their doses reduced due to AEs.

Hematologic adverse events. During the dose-escalation phase, the most common hematologic AEs were anemia and thrombocytopenia (Table 4, Supplemental Table 1). A significant proportion of patients entered the study with abnormal hematologic parameters including Grade 1/2 anemia (78%) and Grade 1/2 thrombocytopenia (49%). During dose expansion, 4 of 11 patients experienced ≥ Grade 3 hematologic AEs possibly related to carfilzomib. Notably, all patients in the dose-expansion phase entered the study with Grade 1/2 anemia, and 4 had Grade 1/2 thrombocytopenia at baseline. Dosing of carfilzomib at 20 mg/m^2 was associated with a transient decrease in platelet counts that recovered during the 12-day rest period at the end of the

cycle (Figure 1A). The effect was more pronounced at 27 mg/m^2, with patients displaying a decrease in platelet counts from 25–50% with the first dose (Figure 1B). Increased occurrences of Grade 3 anemia and Grade 4 thrombocytopenia were observed with carfilzomib doses of ≥20 mg/m^2, although these were the only AEs noted to increase in incidence or severity with dose level. The relative incidence of thrombocytopenia was greater in patients with MM (43%) than in those with NHL/HD (19%). It is worth noting that 6 of the 12 patients who experienced AEs of thrombocytopenia were in the 2 highest dosing groups, where the majority of patients (11 of 14) had MM. Thrombocytopenia was not associated with any bleeding events at any dose in this study.

Non-hematologic adverse events. Non-hematologic AEs were reported in >30% of patients during the dose-escalation phase (Table 4). These events were primarily of Grade 1/2 and were not life-threatening. No occurrences of Grade 3/4 treatment-emergent PN were reported, despite 50% of patients having Grade 1 PN at baseline.

The 27 mg/m^2 dose was associated with reversible Grade 1/2 increases in creatinine in 3/6 patients, generally in association with blood urea nitrogen elevations. In addition, a reversible constellation of symptoms that included fever, chills, and rigors with a mild or moderate (Grade 1/2) increase in creatinine on D2 prior to dosing was observed in 3/5 MM patients receiving the 27 mg/m^2 dose. Elevation of creatinine was reversible and did not recur with carfilzomib rechallenge during subsequent cycles.

In the dose-expansion phase, non-hematologic AEs were reported in >70% of patients. As in the dose-escalation phase, the majority of these events were of Grade 1/2 and were neither severe nor life-threatening (Table 4). Notably, there were no patients with PN, and only 1 patient

reported Grade 1 paraesthesia. Hyperkalemia was observed in 3 patients in the dose-expansion cohort, and will continue to be evaluated in ongoing and future studies to determine its true incidence.

Serious adverse events. Three patients (8%) discontinued treatment during dose escalation with SAEs that were possibly or probably related to carfilzomib, including sepsis (n=1), elevated AST without significant ALT or other liver enzyme elevations (n=1), and chemical pancreatitis (n=1). Two deaths were reported during the study period or within 30 days of the last dose of carfilzomib: 1 patient with MM died of progressive disease, and 1 patient with NHL died of septic shock and renal failure possibly related to both carfilzomib and underlying disease.

Five patients in the expansion cohort (45%) experienced a total of 9 SAEs. Of these events, only 1 (hypoxia) was assessed as related to study drug, although this resolved and did not recur with carfilzomib retreatment. Five patients (19%) continued treatment for >1 year without evidence of cumulative toxicity, and no specific target-organ toxicity was observed during long-term therapy.

Dose-limiting toxicities/maximum tolerated dose. There were 2 DLTs reported in 6 patients enrolled in the 27 mg/m^2 dose level during the study. However, in the final analysis, only one event (Grade 3 hypoxia) was confirmed as meeting the DLT criteria. Among the 8 patients enrolled at the 20 mg/m^2 dose level, 1 case of acute renal failure (Grade 3) occurred in a patient who had Grade 2 elevated creatinine at study enrollment. Based on a preliminary analysis of safety data from the highest dose groups and evidence of anti-myeloma activity at the 27 mg/m^2 dose, the study was subsequently amended to evaluate a conservative escalated dosing approach

from 20 mg/m^2 to 27 mg/m^2 on D8 of the first dosing cycle in the dose-expansion cohorts. This regimen was well tolerated in 6 patients without an observation of a DLT. As a result, the 2 ongoing phase 2 trials (003 and 004) were amended to adopt this new maximum administered dose.

Pharmacokinetics

Because of the a limited number of samples with detectable carfilzomib, insufficient sample volumes, and inaccurate or unconfirmed sample times, PK parameter estimates are reported only for the 11, 15, 20, and 27 mg/m^2 doses (Table 5). High inter- and intrapatient variability in the individual plasma concentrations and maximum plasma concentrations (C_{max}) of carfilzomib were observed, possibly reflecting differences in the rate of administration of carfilzomib and the timing of sample collections. Clearance (CL) was rapid, with a mean elimination half-life ($t_{1/2}$) generally <30 minutes. Because CL was higher than liver blood flow, it can be postulated that significant hepatic clearance of carfilzomib is unlikely. The volume of distribution at steady state (V_{ss}) suggested wide tissue distribution of carfilzomib.

Pharmacodynamics

Carfilzomib induced a dose-dependent inhibition of the 20S chymotrypsin-like proteasome activity 1 hour after dosing on D1. Doses of 15 mg/m^2 resulted in >80% proteasome inhibition in whole blood (Figure 1C) and >70% inhibition in PBMCs (Figure 1D). At 27mg/m^2, ~90% inhibition of proteasome activity was achieved in PBMCs. Minimal recovery of proteasome activity in whole blood between cycles was observed throughout the study, likely due to the inability of erythrocytes to synthesize new proteasome subunits (9). In PBMCs, which

are capable of subunit synthesis, minimal to no recovery in proteasome activity was seen in D2 pre-dose samples, suggesting that prolonged inhibition was achieved with carfilzomib administration (Figure 1E, F). Proteasome inhibition after the second dose was equivalent to or greater than that seen with the first dose in both whole blood and PBMC samples. Substantial recovery of proteasome activity was observed in PBMCs prior to dosing in C2 after a 12-day rest period (Figure 1E, F).

Response

Thirty-six patients were evaluable for response in the dose-escalation portion of the study, and 14 (39%) had objective responses or stabilization of disease (Table 6). Responses of MR or better were observed primarily in patients with MM at doses of 15 mg/m^2 or higher where proteasome inhibition is at least 70%. The patients remained in response between 5 and 14 cycles. No objective responses in patients with NHL/HD were observed.

Nine patients were evaluable for response in the dose-expansion phase. Three of these patients had objective responses, including 2 PR (1 MM, 1 WM), and 1 MR (MM) (Table 6). The 5 patients with MM who achieved responses of PR continued to receive treatment for ≥6 months.

Discussion

Based on the *in vitro* and *in vivo* activity of carfilzomib observed in preclinical studies (9, 13, 20), the current phase 1 study was designed to determine the safety and tolerability of carfilzomib in patients with relapsed and refractory hematologic malignancies using a 28-day dosing cycle. The overall safety profile of carfilzomib administered on this dosing schedule appears to be quite favorable, as carfilzomib doses up to the highest tested dose of 27 mg/m^2

were found to be tolerable and premedication with antiemetics and antidiarrheals was generally not required. The majority of AEs across both phases of the study were Grade 1/2 in severity and generally manageable. There were no episodes of Grade 3/4 PN, despite 24 patients (50%) having entered the study with Grade 1 PN. These findings contrast with those seen with other PIs as well with many other classes of agents (e.g., alkylating agents, thalidomide) used to treat hematologic malignancies (21).

There was a trend for the frequency and severity of the hematologic toxicities to be dose related. Cyclic thrombocytopenia was dose dependent and was observed primarily at the 27 mg/m^2 dose level and to a lesser extent at 20 mg/m^2. This phenomenon has also been observed with bortezomib and is likely to be a PI class effect on platelet budding from megakaryocytes (22). However it is important to note that the majority of the patients with MM enrolled in the present study had low bone marrow reserve due to their rapidly progressing disease. The relative incidence of thrombocytopenia was greater in these patients than in those with NHL/HD, and a significant proportion of these events were attributable to disease progression. At the 27 mg/m^2 dose level, carfilzomib was also associated with a mild, transient, and reversible increase in creatinine, often accompanied by BUN elevations, consistent with a pre-renal etiology. These findings are consistent with an infusion-like reaction. As a result, guidelines were instituted for use in C1 of ongoing carfilzomib studies to address the monitoring and management of infusion-like and renal-related events. These included extending the infusion time from approximately 2 minutes to 10 minutes, and the addition of low-dose dexamethasone (4 mg) prior to administration of carfilzomib. These prophylactic guidelines have contributed to the amelioration of the infusion-like reaction.

The pharmacokinetic properties of carfilzomib were similar to those reported in the 001 trial (14). Clearance of carfilzomib occurred rapidly, and non-compartmental analysis revealed a mean elimination half-life of <30 minutes and no accumulation with repeat dosing. A more prolonged elimination half-life that appears to increase with repeat dosing has been reported for bortezomib, although similarly widespread tissue distribution has been observed (23). The V_{ss} also mirrored observations in the 001 trial, again suggesting a wide tissue distribution (9). High interpatient and intrapatient variability in carfilzomib plasma concentrations were observed, likely due in part to variations in the duration of the IV infusion (2–10 minutes).

Because PK parameters were not likely to guide dosing, given the absence of dose-dependent increases in $C_{max,}$ AUC_{last}, and $t_{½}$, PDn and safety parameters were evaluated more closely. The levels of proteasome inhibition observed with carfilzomib contrast with those achieved using bortezomib on the D1/D4 schedule, where inhibitory activity plateaus at ~60–70% (24). The tolerability of consecutive-day dosing and the irreversible mechanism of carfilzomib result in sustained inhibition of the chymotrypsin-like activity of the proteasome for >48 hours. Because bortezomib-resistant cells have been characterized by the over-expression of proteasome subunits (25), long-lasting, robust inhibition by carfilzomib (9) might overcome resistance induced by this mechanism. Further studies will be needed to elucidate the effect, if any, of bortezomib-resistance on responses to carfilzomib, the impact of carfilzomib on the activity of the immunoproteasome, and the relationship of the extent of proteasome/immunoproteasome inhibition to the likelihood of response (i.e., a dose-response relationship).

While not a primary focus of the study, efficacy results were encouraging. Objective responses or SD were observed in 14 of 36 patients with heavily pretreated hematologic malignancies, including 3 of 6 patients with MM who had failed bortezomib as their last therapy. Responses

generally occurred within the first or second cycle and persisted for >1 year with continued carfilzomib. However, the number of patients was too small, particularly in the dose-expansion portion of the study, to draw any meaningful conclusions. Further studies are needed to assess the effects of the carfilzomib dose and schedule, as well as the addition of dexamethasone (40 mg/week; 120 mg/28-day cycle).

In putting the current findings into perspective with the 001 study, a number of points should be considered. The 001 study employed a more intensive dosing schedule of 5 consecutive days in a 14-day cycle and established a MTD at 15 mg/m^2(14). In the present study, a MTD was not established despite an AE profile that was largely similar to that seen in the 001 study; however, the consecutive day dosing for 3 weeks of a 4-week cycle appears to have comparable, if not improved, tolerability at both 20 and 27 mg/m^2. One notable difference was an apparent numerical increase in AEs, particularly hematologic AEs, with the current dosing schedule. While the number of patients per treatment group precludes a rigorous statistical analysis, there were fewer treatment discontinuations in this study. The efficacy data and PK profiles were similar between the 2 studies, although a direct comparison to the latter is technically challenging due to the high intra-study variability and the PK properties of the drug.

Despite substantial inhibition of proteasome activity, long-term tolerability of carfilzomib was achieved without observed cumulative toxicities, and several patients remained on therapy for >1 year. Ongoing studies in larger patient populations support these observations (26, 27). Based on these data, carfilzomib appears to offer a potentially non–cross-resistant mechanism of action with a favorable toxicity profile. The escalated dosing schedule, as employed in the dose-expansion phase, was likely a contributing factor to the safety and tolerability seen in this study. The phase 1 observations presented herein, along with those from the earlier 001 study, provide a

strong rationale for the dosing regimens and schedules for ongoing phase 2 studies in patients with MM, as well as in patients with other hematologic malignancies or solid tumors. These studies include PX-171-003, which evaluated the efficacy of single-agent carfilzomib in patients with relapsed and refractory MM, and PX-171-004, which evaluated the efficacy of single-agent carfilzomib in patients with relapsed MM.

Acknowledgments

This study was conducted by Melissa Alsina (H. Lee Moffitt Cancer and Research Center, Tampa, FL, USA), Richard R. Furman (Weill Cornell Medical College, New York, NY), Andre Goy (John Theurer Cancer Center, Hackensack, NJ, USA), Peter J. Rosen (Tower Cancer Research Foundation, Beverly Hills, CA, USA), and Suzanne Trudel (University of Toronto Princess Margaret Hospital, Toronto, ON, Canada), and supported by Onyx Pharmaceuticals, Inc. The authors would like to thank the patients, the additional study investigators, and the participating institutions. Statistical support was provided by Gerard Smits (Onyx Pharmaceuticals), critical review by Tom Renau, PhD (Onyx Pharmaceuticals), and editorial assistance by Brian Szente, PhD (Fishawack Communications) supported by Onyx Pharmaceuticals. Melissa Alsina, Richard R. Furman, Andre Goy, Peter J. Rosen, and Suzanne Trudel have no financial interest in the development of carfilzomib.

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Figure Legend

Figure 1. Cyclic thrombocytopenia in patients treated with carfilzomib and dose-dependent inhibition of proteasome chymotrypsin-like activity in whole blood and PBMCs. Results are shown for individual patients treated at 20 mg/m^2 (A) and 27 mg/m^2 (B). Chymotrypsin-like specific proteasome activity was measured in whole blood (C) and PBMCs (D) determined 1 hour after the first dose of carfilzomib (Cycle 1, Day 1). The percent proteasome activity for each patient was calculated by comparing the activity in the samples taken 1 hour after dosing with the specific activity measured in the samples taken prior to dosing. The mean percent proteasome activity and the standard error are plotted at each dose level. An expanded time course of proteasome activity in PBMCs pre-dose and 1 hour post-dose for Cycle 1, Days 1, 2, and 8 and Cycle 2 Day 1 is shown for individual patients treated at either 20 mg/m^2 (E) or 27 mg/m^2 (F).

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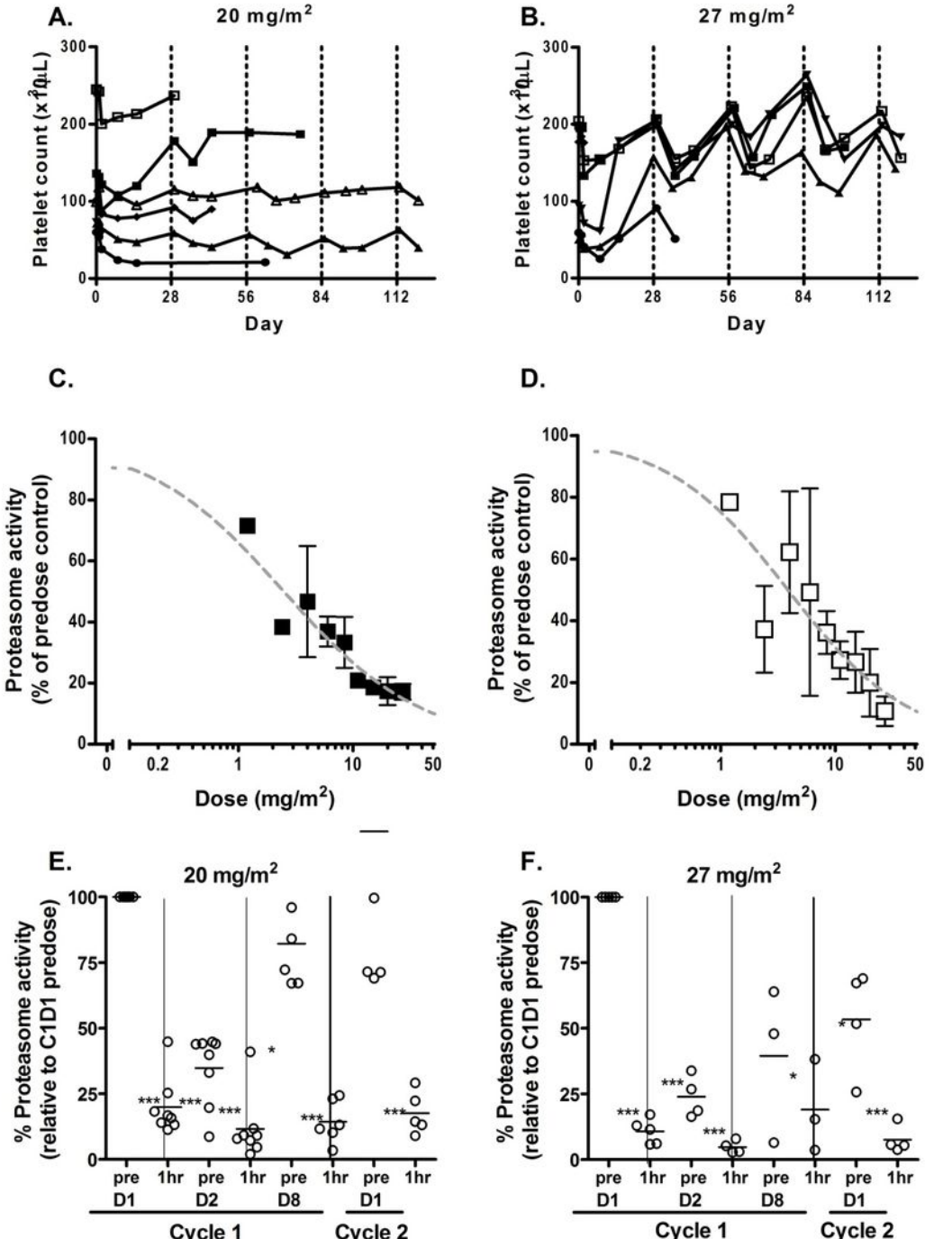

Table 1. Criteria for dose-limiting toxicities

Qualifying event
Study drug-related AEs occurring in the first 28 days of study participation and any of the following:
1. > Grade 3 nausea, vomiting, or diarrhea not controlled by antiemetic/antidiarrheal therapy
2. > Grade 2 neuropathy with pain
3. Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) lasting >14 days without growth factor support
4. Febrile neutropenia (ANC $<1.0 \times 10^9$/L with fever $\geq 38.3^{\circ}$C)
5. Grade 4 thrombocytopenia ($<25.0 \times 10^9$/L) lasting >7 days or associated with bleeding
6. Other non-hematologic toxicity $\geq$Grade 3

Table 2. Patient Demographics

Characteristic	Dose escalation (N=37)	Expansion (N=11)
Age (years)		
Median	61.4	65.0
Range	25–82	38–77
Sex, n (%)		
Male	20 (54.1)	6 (54.5)
Female	17 (45.9)	5 (45.5)
Race/ethnicity, n (%)		
Caucasian	33 (89.2)	9 (81.8)
African American	1 (2.7)	2 (18.2)
Hispanic	1 (2.7)	---
Other	2 (5.4)	---
Diagnosis, n (%)		
Multiple myeloma	21 (56.8)	7 (63.6)
Secretory	19 (51.4)	7 (63.6)
Non-secretory	2 (5.4)	---
Lymphoma	16 (43.2)	2 (18.2)
Mantle cell	6 (16.2)	---
Follicular	6 (16.2)	---
Diffuse large cell	2 (5.4)	1 (9.1)
T-cell	---	1 (9.1)
SLL/CLL	1 (2.7)	---
Hodgkin lymphoma	1 (2.7)	---
Waldenström's macroglobulinemia	---	2 (18.2)
Years since diagnosis		
Median	3.9	7.0
Range	0.7–13.7	3.1–22.9

MM, multiple myeloma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia.

Author Manuscript Published OnlineFirst on July 3, 2012; DOI: 10.1158/1078-0432.CCR-11-3007
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Table 3A. Patient Diagnosis and Carfilzomib Dose Cohorts (Dose escalation)

	Dose Cohort									
	1.2 mg/m^2 (n=3)	**2.4 mg/m^2 (n=3)**	**4.0 mg/m^2 (n=4)**	**6.0 mg/m^2 (n=3)**	**8.4 mg/m^2 (n=3)**	**11.0 mg/m^2 (n=4)**	**15.0 mg/m^2 (n=3)**	**20.0 mg/m^2 (n=8)**	**27.0 mg/m^2 (n=6)**	**All patients (N=37)**
Diagnosis										
MM	0	3	0	2	1	2	2	6	5	21
NHL	3	0	3	1	2	2	1	2	1	15
HL	0	0	1	0	0	0	0	0	0	1
Cycles* per patient										
Mean	2.0	5.7	4.5	4.7	4.3	3.0	5.7	2.0	5.5	3.9
Range	1.0–4.0	1.0–14.0	0.0–14.0	1.0–12.0	2.0–9.0	2.0–6.0	1.0–14.0	0.0–7.0	0.0–10.0	0.0–14.0
Cumulative dose, mg/m^2										
Median	14	270	202	330	339	253	595	285	820	132
Range	7–29	14–766	16–692	30–912	84–833	132–572	75–1530	40–920	54–1566	7–1566

CFZ, carfilzomib; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma
*Includes patients with multiple dose escalations to higher dose levels

Table 3B. Patient Diagnosis and Carfilzomib Dose Cohorts (Dose-expansion)

	Dose Cohort	
N=11 patients	**20/27 mg/m^2 (n=7)**	**20/27 mg/m^2 + Dex (n=4)**
Diagnosis		
MM (n=7)	3	4
NHL (n=2)	2	0
WM (n=2)	2	0
Cycles per patient		
Mean	3.9	4.0
Range	1.0–12.0	1.0–12.0
Cumulative dose, mg/m^2		
Median	282	168
Range	80–1903	70–1848

CFZ, carfilzomib; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; WM, Waldenström's macroglobulinemia

Table 4. Treatment-emergent Adverse Events, Regardless of Relationship to Carfilzomib Treatment, Reported in ≥20% of Patients or Related to Carfilzomib Occurring in ≥5% of Patients

Adverse event	Dose escalation (N=37)				Dose expansion (N=11)			
	All grades, n (%)		≥ Grade 3, n (%)		All grades, n (%)		≥ Grade 3, n (%)	
	All cause	Related	All cause	Related	All cause	Related	All cause	Related
Any	37 (100)	32 (87)	26 (70)	13 (35)	11 (100)	10 (91)	9 (82)	4 (36)
Hematologic events								
Anemia	17 (46)	5 (14)	10 (27)	4 (11)	8 (73)	7 (64)	5 (45)	4 (36)
Thrombocytopenia	12 (32)	4 (11)	10 (27)	4 (11)	7 (64)	6 (55)	4 (36)	3 (27)
Neutropenia	4 (11)	1 (3)	2 (5)	1 (3)	3 (27)	3 (27)	1 (9)	1 (9)
Leukopenia	1 (3)	1 (3)	1 (3)	1 (3)	2 (18)	2 (18)	---	---
Non-hematologic events								
Nausea	22 (59)	14 (38)	1 (3)	---	3 (27)	3 (27)	---	---
Fatigue	19 (51)	11 (30)	4 (11)	2 (5)	5 (45)	5 (45)	---	---
Constipation	16 (43)	4 (11)	---	---	2 (18)	1 (9)	---	---
Pyrexia	15 (41)	9 (24)	---	---	3 (27)	---	---	---
Cough	14 (38)	5 (14)	---	---	4 (36)	---	---	---
Vomiting	13 (35)	9 (24)	---	---	1 (9)	1 (9)	---	---
Anorexia	12 (32)	5 (14)	---	---	1 (9)	1 (9)	---	---
Diarrhea	12 (32)	7 (19)	3 (8)	---	5 (45)	2 (18)	---	---
Dyspnea	12 (32)	2 (5)	1 (3)	---	2 (18)	1 (9)	---	---
Headache	11 (30)	3 (8)	---	---	2 (18)	2 (18)	---	---
Upper respiratory tract infection	10 (27)	4 (11)	---	---	2 (18)	---	---	---
Increased serum creatinine	9 (24)	5 (14)	1 (3)	---	3 (27)	3 (27)	---	---
Hyperglycemia	8 (22)	---	1 (3)	---	2 (18)	---	1 (9)	---
Shoulder pain	8 (22)	---	---	---	---	---	---	---
Chills	7 (19)	6 (16)	---	---	2 (18)	1 (9)	---	---
Insomnia	7 (19)	3 (8)	---	---	4 (36)	1 (9)	---	---
Peripheral edema	7 (19)	1 (3)	---	---	3 (27)	---	1 (9)	
Peripheral neuropathy	6 (16)	5 (14)	---	---	1 (9)	---	---	---

Pharyngolaryngeal pain	6 (16)	4 (11)	---	---	2 (18)	---	---	---
Hyperkalemia	---	---	---	---	3 (27)	2 (18)	1 (9)	---
Hypoalbuminemia	1 (3)	---	---	---	3 (27)	---	3 (27)	---

Table 5. Pharmacokinetic Parameters for Carfilzomib (11, 15, 20, and 27 mg/m^2 on Cycle 1, Day 1)

	11 mg/m^2 n=3	15 mg/m^2 n=3	20 mg/m^2 n=8	27 mg/m^2 n=5
C_{max}, ng/mL				
Mean	505	143	528	406
SD	±485	±97	±406	±517
$t_{1/2}$, minutes				
Mean	12.9	13.1	39.4	26.8
SD	±6.5	±3.6	±28.8	±4.7
CL, mL/minute				
Mean	10437	30342	10979	74575
SD	±10973	±23890	±5880	±108935
V_{ss}, L				
Mean	68.4	199.1	108.4	1539
SD	±79.5	±116.6	±71.2	±2862
AUC_{last}, ng·min/mL				
Mean	4049	1414	4911	3409
SD	±3695	±919	±3495	±3964

AUC_{last}, area under curve to last measurable time point (includes C_0); CL, systemic clearance; C_{max}, maximum plasma concentration; SD, standard deviation; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady state

Table 6. Carfilzomib Responses in Multiple Myeloma, Waldenström's Macroglobulinemia, and non-Hodgkin Lymphoma Patients

Patient ID, by disease* category	Response	Disease subtype	Starting dose (mg/m^2)	Dose at discontinuation (mg/m^2)	Duration on study (days)	Last prior treatment
Dose-escalation						
MM (n=20)						
2-02-004	SD		2.4	20	409	BTZ
2-06-002	SD	IgG	6.0	20	71	BTZ / Dex
2-01-005	PR	IgG	15	20	392	SCT
2-01-007	SD	IgG	20	20	62	CTX/ Pred
2-01-008	PR	IgG	20	20	224	BTZ
2-01-009	PR	IgA	27	27	334	BTZ/tipifarnib
2-01-011	MR	IgG	27	27	134	Len / Dex
2-01-012	PR	IgG	27	20	259	BTZ
2-06-004	SD	IgG	27	27	225	CTX/ Pred
NHL (n=15)						
2-02-008	SD	FL	4.0	20	387	NA
2-02-010	SD	FL	6.0	20	352	NA
2-02-011	SD	SLL/CLL	8.4	20	317	NA
2-02-012	SD	FL	11	11	68	NA
2-02-021	SD	FL	20	20	128	NA
Dose-expansion						
MM (n=6)						
2-01-020	PR	IgG	20/27	20/27	324	Thal/Dex
2-31-001	MR	IgG	20/27 + Dex	20/27 + Dex	324	BTZ/Dex/ PD0332991
2-01-019	SD	IgG	20/27	20/27	121	Sorafenib
WM (n=2)						
2-07-001	PR	IgM	20/27	20/27	156	Rituximab
2-31-003	SD	IgM	20/27	20/27	67	BTZ/Dex/CTX

BTZ, bortezomib; CFZ, carfilzomib; CTX, cyclophosphamide; Dex, dexamethasone; Gem, gemcitabine; Len, lenalidomide; MM, multiple myeloma; MR, minimal response; NA, not applicable; NHL, non-Hodgkin lymphoma; PR, partial response; Pred, prednisone; SCT, stem cell transplant; SD, stable disease; WM, Waldenström's macroglobulinemia.

*The single patient with HL was not a responder and is not included in the table.

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A phase 1 single-agent study of twice-weekly consecutive-day dosing of the proteasome inhibitor carfilzomib in patients with relapsed or refractory multiple myeloma or lymphoma

Melissa Alsina, Suzanne Trudel, Richard R. Furman, et al.

Clin Cancer Res Published OnlineFirst July 3, 2012.