Clinical Cancer Research

A Phase Ib/II Study of Oprozomib in Patients with Advanced Multiple Myeloma and Waldenström Macroglobulinemia

Irene M. Ghobrial[1], Ravi Vij[2], David Siegel[3], Ashraf Badros[4], Jonathan Kaufman[5], Noopur Raje[6], Andrzej Jakubowiak[7], Michael R. Savona[8], Mihaela Obreja[9], and Jesus G. Berdeja[10]

Abstract

Purpose: The oral proteasome inhibitor oprozomib has shown preclinical antitumor activity. Here, we report phase Ib/II study results investigating single-agent oprozomib in patients with relapsed multiple myeloma and Waldenström macroglobulinemia.

Patients and Methods: The primary objectives were to determine the MTD, safety, and tolerability of oprozomib (phase Ib) as well as overall response rate (ORR; phase II). Oprozomib was administered once daily on days 1, 2, 8, and 9 (2/7 schedule) or days 1 to 5 (5/14 schedule) of a 14-day cycle.

Results: In patients with multiple myeloma or Waldenström macroglobulinemia ($n = 71$), the determined MTDs were 300 mg/day (2/7 schedule) and 240 mg/day (5/14 schedule). Median oprozomib treatment duration for patients with multiple myeloma was 11.4 weeks (2/7 schedule, 240/300 mg/day), 5.4 weeks (5/14, 240 mg/day), and 10.1 weeks (5/14, 150/180 mg/day). For patients with Waldenström macroglobulinemia, these values were 34.6 weeks (2/7 schedule, 240/300 mg/day) and 8.1 weeks (5/14 schedule, 240 mg/day). The most common grade $\geq$3 adverse events (AE) in phase Ib included gastrointestinal and hematologic AEs. Three AE-related deaths in phase II prompted enrollment into 2/7 and 5/14 step-up dosing schedules (240/300 mg/day and 150/180 mg/day, respectively). In phase II, ORRs in 95 response-eligible multiple myeloma patients were 41.0%, 28.1%, and 25.0% in the 2/7, 240/300-mg/day; 5/14, 150/180-mg/day; and 5/14, 240-mg/day cohorts, respectively. ORRs in 31 response-eligible Waldenström macroglobulinemia patients were 71.4% and 47.1% for the 2/7 and 5/14 cohorts, respectively.

Conclusions: This study demonstrated promising efficacy of single-agent oprozomib in patients with relapsed multiple myeloma and Waldenström macroglobulinemia.

Introduction

Proteasome inhibitors (PI), including carfilzomib, bortezomib, and ixazomib, have become validated strategies for treating patients with multiple myeloma. Bortezomib has demonstrated efficacy in patients with multiple myeloma, but is associated with peripheral neuropathy and must be administered intravenously or subcutaneously, limiting its use in some patients (1–5). Given the challenges of intravenous administration, subcutaneous treatment with bortezomib is now the preferred administration route (6). Carfilzomib, an epoxyketone PI, is approved in the United States and other countries for the treatment of relapsed or refractory multiple myeloma (7). In the ENDEAVOR trial, carfilzomib demonstrated superiority over bortezomib in patients with relapsed or refractory multiple myeloma (8). One challenge associated with carfilzomib treatment is the need for twice-weekly intravenous administration (7, 9). Once-weekly carfilzomib has recently been approved for the treatment of relapsed or refractory multiple myeloma based on results from the phase III A.R.R.O.W. trial, which demonstrated prolonged progression-free survival (PFS) with once-weekly carfilzomib at 70 mg/m^2 versus twice-weekly carfilzomib at 27 mg/m^2 (7, 10).

Oral administration of PIs can enhance accessibility and feasibility of multiple myeloma treatment. Ixazomib is the only oral PI that is currently approved in the United States for the treatment of multiple myeloma (11). In the phase III TOURMALINE-MM1 trial, the addition of ixazomib to lenalidomide and dexamethasone significantly improved PFS compared with lenalidomide-dexamethasone (12). In a subgroup analysis of TOURMALINE-MM1, however, patients with 1 prior therapy and transplant did not have a PFS improvement with ixazomib-lenalidomide-dexamethasone (13).

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts. [2]Department of Medicine, Washington University School of Medicine, St Louis, Missouri. [3]Myeloma Division, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, New Jersey. [4]Multiple Myeloma Service, University of Maryland School of Medicine, Baltimore, Maryland. [5]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Emory University, Atlanta, Georgia. [6]Department of Hematology/Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts. [7]Myeloma Program, University of Chicago Medical Center, Chicago, Illinois. [8]Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee. [9]Department of Biostatistics, Amgen Inc., Thousand Oaks, California. [10]Myeloma Research, Sarah Cannon Research Institute, Nashville, Tennessee.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Irene M. Ghobrial, Dana-Farber Cancer Institute; 450 Brookline Avenue, Boston, MA 02215. Phone: 617-632-4218; Fax: 617-582-8606; E-mail: Irene_ghobrial@DFCI.Harvard.edu

Clin Cancer Res 2019;25:4907–16

doi: 10.1158/1078-0432.CCR-18-3728

Translational Relevance

This study is the first to evaluate single-agent oprozomib, an oral proteasome inhibitor, in patients with relapsed multiple myeloma and Waldenström macroglobulinemia. The data from this study demonstrated that oprozomib had promising antitumor activity in patients with relapsed multiple myeloma or Waldenström macroglobulinemia, including responses observed in patients refractory to other proteasome inhibitors (bortezomib or carfilzomib). Gastrointestinal tolerability was a concern with the formulation of oprozomib used in this study, and alternative formulations are currently being investigated to improve tolerability. Overall, the findings from this study provide proof of principle for the single-agent activity of oprozomib in relapsed multiple myeloma or Waldenström macroglobulinemia and provide rationale for the evaluation of new oprozomib formulations and oprozomib-based combination therapy for the treatment of patients with multiple myeloma or Waldenström macroglobulinemia.

Because of the limitations and challenges of the 3 PIs currently approved for multiple myeloma treatment, there is a need for additional PIs that are effective, tolerable, and convenient. Oprozomib is an oral tripeptide epoxyketone PI that is structurally analogous to carfilzomib and binds selectively and irreversibly to the proteasome (14). Oprozomib has shown antitumor activity similar to carfilzomib in preclinical models (14–16). Oprozomib inhibited chymotrypsin-like (CT-L) activity in human multiple myeloma cell lines, and a significant decrease in multiple myeloma cell viability occurred in response to oprozomib treatment in *in vivo* mouse models (15). Oprozomib also inhibited CT-L activity and induced toxicity in primary Waldenström macroglobulinemia cells from previously treated patients with Waldenström macroglobulinemia (16). In a phase I study of patients with refractory or recurrent solid tumors, single-agent oprozomib had pharmacokinetic and pharmacodynamic properties similar to carfilzomib, with proteasome inhibition of $\geq$80% in the majority of patients (17). Herein, we describe final results from a phase Ib/II study investigating single-agent oprozomib in patients with relapsed multiple myeloma and Waldenström macroglobulinemia.

Patients and Methods

Study design and treatment

This was a multicenter, open-label, phase Ib/II study (NCT01416428). In phase Ib, the primary objectives were to determine the MTD of single-agent oprozomib and to evaluate the safety/tolerability of oprozomib in patients with hematologic malignancies. In phase II, the primary objective was to determine the overall response rate (ORR), and the secondary objectives were to determine the duration of response and clinical benefit rate in patients with multiple myeloma, major response rates in patients with Waldenström macroglobulinemia, and PFS, and to define oprozomib pharmacokinetics and assess safety. Exploratory endpoints included evaluation of oprozomib pharmacodynamics. Dates of enrollment were from November 11, 2011, to January 22, 2014, for phase Ib and from October 11, 2013, to June 26, 2015, for phase II.

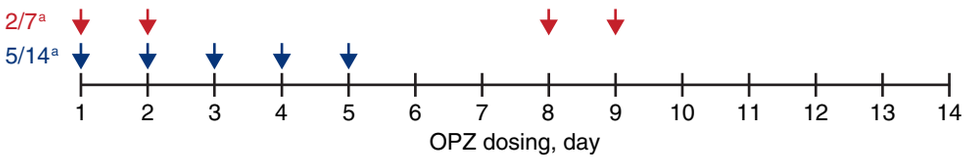
The phase Ib dose escalation plan followed a standard 3 + 3 study design. In accordance with the original protocol, oprozomib was administered in split dosing as a powder-in-capsule (PIC; 30 or 120 mg); the first dose was followed by a second dose 4 to 6 hours later for 5 consecutive days (days 1–5) of a 14-day treatment cycle (i.e., 5/14 treatment schedule). The starting dose was 120 mg/day, based on interim results of a phase I study of oprozomib capsules in patients with refractory solid tumors (17). Subsequent cohorts were escalated by 30 mg increments up to 210 mg. A protocol amendment in July 2012 enabled administration of oprozomib tablets (60, 90, or 120 mg; modified-release tablet formulation) once daily on the 5/14 treatment schedule or on days 1, 2, 8, and 9 (i.e., 2/7 treatment schedule) of a 14-day cycle. The starting dose was amended to 150 mg/day, based on the safety results from the PIC cohorts at the time the tablet was introduced. Oprozomib doses were subsequently escalated by 30-mg increments in each cohort, up to 330 mg/day (Fig. 1).

In the phase II portion of the study, patients on the 5/14 schedule received oprozomib at a dose of 240 mg/day (MTD, see Results). A subsequent protocol amendment to test alternate regimens and lower doses allowed patients to enroll in a step-up dosing scheme where patients received 150 mg/day in cycle 1, stepped-up to a target dose of 180 mg/day thereafter (i.e., 150/180 mg/day). Per the protocol amendment, patients receiving oprozomib on the 2/7 schedule in the phase II portion received oprozomib in a step-up dosing scheme of 240/300 mg/day. Oprozomib was administered to patients in the fasted state ($\geq$2 hours since the previous meal and fasting for $\geq$2 hours after dosing) in cycle 1, and after a meal in cycle 2 and subsequent cycles.

Several treatments were required during the administration of oprozomib to mitigate potential side effects. Among these, aprepitant or fosaprepitant were recommended as additional antinausea agents to be used in the event of persistent nausea. For patients developing any-grade diarrhea, loperamide was recommended to be administered at the first sign of symptoms. For patients with persistent diarrhea despite the use of loperamide, diphenoxylate and atropine were strongly recommended, although other antidiarrheal agents were permitted as necessary. Following a protocol amendment in June 2013, valacyclovir (or equivalent antiviral medication) was required to prevent herpes zoster infection. Oral hydration of 1.5–2 L/24 hours was to be instituted for all patients 24 to 48 hours prior to the start of each cycle and was to be continued every day of oprozomib dosing under the June 2013 protocol amendment. All patients were required to receive premedication with a 5-hydroxytryptamine-3 inhibitor (such as ondansetron or granisetron) prior to each dose of oprozomib, with additional doses administered as needed throughout the day during the cycle. Low-dose dexamethasone (4 mg) was also given $\geq$30 minutes prior to oprozomib dosing. Oprozomib treatment was to be continued until disease progression or unacceptable toxicity.

Patients

Adult patients ($\geq$18 years of age) with hematologic malignancies (excluding acute leukemia or myelodysplastic syndrome) who relapsed after receiving $\geq$1 line of therapy were eligible to enter the phase Ib portion of the study. The phase II portion only enrolled patients with multiple myeloma or Waldenström macroglobulinemia. Other inclusion criteria included Eastern Cooperative Oncology Group performance status 0–2; adequate



		Patient cohorts											
		1 (*n* = 3)	2 (*n* = 4)	3 (*n* = 3)	4 (*n* = 7)	5 (*n* = 3)	6 (*n* = 7)	7 (*n* = 3)	8 (*n* = 8)	9 (*n* = 3)	10 (*n* = 6)	11 (*n* = 7)	12 (*n* = 3)
Schedule	2/7	●		●		●		●		●		●	●
	5/14		●		●		●		●		●		
Daily dose	150 mg	●	●										
	180 mg			●	●								
	210 mg					●	●						
	240 mg							●	●				
	270 mg									●	●		
	300 mg											●	
	330 mg												●
Planned cumulative treatment exposure per 14-day cycle		600 mg	750 mg	720 mg	900 mg	840 mg	1,050 mg	960 mg	1,200 mg	1,080 mg	1,350 mg	1,200 mg	1,320 mg

Figure 1.

Oprozomib (OPZ) dosing schedule and dose-level cohorts in the phase Ib portion of the study. [a]Oprozomib given orally once daily on days 1, 2, 8, and 9 (2/7) or days 1 to 5 (5/14) of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.

cardiovascular function without New York Heart Association (NYHA) class III or IV congestive heart failure, symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction in the previous 6 months prior to first dose of study drug; and adequate renal function, with calculated or measured creatinine clearance rate of ≥30 mL/minute (Cockcroft and Gault formula). Exclusion criteria included history of previous clinically significant gastrointestinal bleed in the last 6 months prior to the first dose of study drug. Additional inclusion and exclusion criteria are listed in Supplementary Methods.

The study was conducted in accordance with the Declaration of Helsinki. Institutional review board/independent ethics committee approval was obtained at each site and all patients provided written, informed consent.

Assessments

The incidence, nature, severity, and relatedness of adverse events (AE) were graded in accordance with the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

For each dosing schedule, the MTD was defined as the highest dose at which a DLT was observed in fewer than 2 of 6 patients (≥6 patients must have been treated at the MTD for a minimum of 1 cycle to establish this dose as tolerated). Response to oprozomib in patients with multiple myeloma was assessed according to International Myeloma Working Group Uniform Response Criteria (18), and response in patients with Waldenström macroglobulinemia was evaluated according to guidelines of the Sixth International Workshop on Waldenström Macroglobulinemia (19).

For pharmacokinetic evaluation, blood samples were drawn at predose and at time points up to 24 hours postdose. Pharmacokinetic analyses included the measurement of maximum plasma concentration (C_{max}), time of maximum plasma concentration (t_{max}), and area under the plasma concentration–time curve (AUC). To assess oprozomib pharmacodynamics, blood samples were drawn. A fluorogenic substrate assay or ELISA was used to measure proteasome activity in red blood cells. Proteasome subunit occupancy was determined via a novel proteasome constitutive/immunoproteasome subunit ELISA (20).

Statistical analyses

The safety-evaluable population included all patients who received ≥1 dose of oprozomib. All safety analyses were performed using this population, defined by cohort or schedule, as appropriate. Safety was assessed through summaries of treatment exposure, DLTs, and AEs. Extent of exposure to the study treatment was summarized using descriptive statistics. All AEs occurring on or after treatment on cycle 1 day 1 were summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), and the NCI-CTCAE version 4.03. The response-evaluable population included patients in the safety population who had ≥1 postbaseline disease assessment or who discontinued because of an AE before first postbaseline disease assessment. For patients with multiple myeloma, ORR was defined as the rate of patients with at least partial response; for patients with Waldenström macroglobulinemia, ORR was defined as the rate of patients with at least minimal response. Clinical benefit rate for multiple myeloma was defined as ORR plus minimal response, and major response rate for Waldenström macroglobulinemia was defined as partial response or better. The Clopper–Pearson method was used to estimate the 95% confidence interval for each ORR. PFS analyses were performed by the Kaplan–Meier method.

Data were collected, analyzed, and interpreted by the authors and the sponsor. All authors had full access to the primary clinical trial data and agreed to be accountable for the accuracy and integrity of the data and analyses.

Data sharing

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing.

Table 1. Patient baseline and disease characteristics by dose-level cohort

	Phase Ib		Phase II				
	MM or WM		MM			WM	
Characteristic	2/7 schedule, 150–330 mg/day ($n = 29$)	5/14 schedule, 120–270 mg/day ($n = 42$)	2/7 schedule, 240/300 mg/day ($n = 41$)	5/14 schedule, 150/180 mg/day ($n = 34$)	5/14 schedule, 240 mg/day ($n = 27$)	2/7 schedule, 240/300 mg/day ($n = 15$)	5/14 schedule, 240 mg/day ($n = 17$)
Median age, years (range)	62.0 (42–80)	63.0 (48–81)	65.0 (47–77)	64.5 (36–85)	63.0 (47–80)	65.0 (58–80)	62.0 (44–85)
Sex, *n* (%)							
Male	17 (58.6)	23 (54.8)	20 (48.8)	21 (61.8)	17 (63.0)	12 (80.0)	12 (70.6)
Female	12 (41.4)	19 (45.2)	21 (51.2)	13 (38.2)	10 (37.0)	3 (20.0)	5 (29.4)
Race, *n* (%)							
Black	5 (17.2)	4 (9.5)	6 (14.6)	7 (20.6)	9 (33.3)	1 (6.7)	0
White	24 (82.8)	36 (85.7)	33 (80.5)	25 (73.5)	17 (63.0)	14 (93.3)	17 (100.0)
Asian	0	2 (4.8)	0	2 (5.9)	1 (3.7)	0	0
Other	0	0	2 (4.9)	0	0	0	0
ECOG PS, *n* (%)							
0	8 (27.6)	14 (33.3)	20 (48.8)	13 (38.2)	8 (29.6)	7 (46.7)	10 (58.8)
1	21 (72.4)	27 (64.3)	19 (46.3)	20 (58.8)	17 (63.0)	7 (46.7)	6 (35.3)
2	0	1 (2.4)	2 (4.9)	1 (2.9)	2 (7.4)	1 (6.7)	1 (5.9)
Median years since diagnosis (range)	4.4 (1–12)	5.2 (1–12)	5.1 (1–18)	4.4 (1–14)	4.9 (2–16)	5.8 (1–14)	7.9 (1–23)
Median number of prior regimens (range)	3.0 (1–8)	3.0 (1–9)	4.0 (1–12)	3.0 (1–10)	5.0 (1–14)	2.0 (1–8)	3.0 (1–7)
Received bortezomib, *n* (%)	23 (79.3)	34 (81.0)	37 (90.2)	33 (97.1)	26 (96.3)	8 (53.3)	13 (76.5)
Bortezomib refractory	13 (44.8)	24 (57.1)	29 (70.7)	21 (61.8)	19 (70.4)	3 (20.0)	4 (23.5)
Received lenalidomide, *n* (%)	19 (65.5)	27 (64.3)	40 (97.6)	31 (91.2)	26 (96.3)	1 (6.7)	2 (11.8)
Lenalidomide refractory	15 (51.7)	21 (50.0)	32 (78.0)	25 (73.5)	20 (74.1)	0	1 (5.9)
Received pomalidomide, *n* (%)	2 (6.9)	0	22 (53.7)	15 (44.1)	14 (51.9)	0	1 (5.9)
Pomalidomide refractory	2 (6.9)	0	19 (46.3)	15 (44.1)	13 (48.1)	0	0
Received prior transplant, *n* (%)	19 (65.5)	31 (73.8)	28 (68.3)	22 (64.7)	23 (85.2)	0	0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MM, multiple myeloma; WM, Waldenström macroglobulinemia.

Results

Patients, enrollment, and treatment

The phase Ib portion of the study enrolled 71 patients with multiple myeloma or Waldenström macroglobulinemia (Supplementary Fig. S1A). Patient baseline and disease characteristics are shown in Table 1. Among patients in the phase Ib portion, the median patient ages were 62.0 years (2/7 schedule) and 63.0 years (5/14 schedule), and patients had received a median of 3 prior regimens of therapy (range, 1–9; Table 1). In phase Ib, all patients with multiple myeloma on the 2/7 schedule ($n = 21$) received oprozomib tablets; in the 5/14 schedule, 20 patients received oprozomib tablets and 11 patients received oprozomib PIC. All patients with Waldenström macroglobulinemia on both 2/7 ($n = 8$) and 5/14 ($n = 11$) schedules in phase Ib received oprozomib tablets.

The phase II portion of the study enrolled 135 patients, including 102 patients with multiple myeloma and 33 with Waldenström macroglobulinemia (Supplementary Fig. S1B). Median patient ages for patients with multiple myeloma were 65.0 years (2/7, 240/300 mg/day), 64.5 years (5/14, 150/180 mg/day), and 63.0 years (5/14, 240 mg/day). For patients with Waldenström macroglobulinemia, median patient ages were 65.0 years (2/7, 240/300 mg/day) and 62.0 years (5/14, 240 mg/day; Table 1). Patients with multiple myeloma had received a median of 4 (range, 1–12) prior regimens of therapy in the 2/7 schedule, 240/300-mg/day cohort, 5 prior regimens (range, 1–14) in the 5/14, 240-mg/day cohort, and 3 prior regimens (range, 1–10) in the 5/14, 150/180-mg/day cohort. Patients with Waldenström macroglobulinemia had received a median of 2 (range, 1–8) prior regimens in the 2/7 schedule, 240/300-mg/day cohort and 3 (range, 1–7) prior regimens in the 5/14, 240-mg/day cohort. In phase II, all multiple myeloma patients on both 2/7 ($n = 41$) and 5/14 ($n = 61$) schedules received oprozomib tablets. All patients with Waldenström macroglobulinemia on both 2/7 ($n = 15$) and 5/14 ($n = 17$) schedules in phase II received oprozomib tablets.

Median oprozomib treatment duration for patients with multiple myeloma was 11.4 (range, 0–88) weeks in the 2/7 schedule, 240/300-mg/day cohort, 5.4 (range, 1–49) weeks in the 5/14, 240-mg/day cohort, and 10.1 (range, 3–83) weeks in the 5/14, 150/180-mg/day cohort. For patients with Waldenström macroglobulinemia, median oprozomib treatment durations were 34.6 (range, 0–91) weeks (2/7 schedule, 240/300-mg/day) and 8.1 (range, 1–128) weeks (5/14 schedule, 240-mg/day). The maximum number of cycles patients with multiple myeloma received oprozomib was 44 for the 2/7, 240/300-mg/day schedule, 42 for the 5/14, 150/180-mg/day schedule, and 25 for the 5/14, 240-mg/day schedule. The maximum number of cycles patients with Waldenström macroglobulinemia received oprozomib was 44 for the 2/7, 240/300-mg/day schedule and 61 for the 5/14, 240-mg/day schedule.

Safety

In phase Ib, 3 patients on the 2/7 schedule reported DLTs: diarrhea (multiple myeloma; 330 mg/day; $n = 1$), thrombocytopenia (multiple myeloma; 330 mg/day; $n = 1$), and hypotension (multiple myeloma; 300 mg/day; $n = 1$; Supplementary Table S1). Four patients on the 5/14 schedule reported DLTs: renal failure (multiple myeloma; 180 mg/day; $n = 1$), tumor lysis syndrome (multiple myeloma; 240 mg/day; $n = 1$), tumor lysis syndrome (Waldenström macroglobulinemia; 240 mg/day; $n = 1$), and vomiting (Waldenström macroglobulinemia; 270 mg/day; $n = 1$). The MTD of single-agent oprozomib was

Table 2. Patient disposition

	Phase Ib		Phase II				
	MM or WM		MM			WM	
	2/7 schedule, 150–330 mg/day ($n = 29$)	5/14 schedule, 120–270 mg/day ($n = 42$)	2/7 schedule, 240/300 mg/day ($n = 41$)	5/14 schedule, 150/180 mg/day ($n = 34$)	5/14 schedule, 240 mg/day ($n = 27$)	2/7 schedule, 240/300 mg/day ($n = 15$)	5/14 schedule, 240 mg/day ($n = 17$)
Patients who discontinued study treatment, *n* (%)	28 (96.6)	38 (90.5)	39 (95.1)	31 (91.2)	27 (100.0)	12 (80.0)	16 (94.1)
Reasons for treatment discontinuations, *n* (%)							
AE	5 (17.2)	8 (19.0)	16 (39.0)	4 (11.8)	12 (44.4)	2 (13.3)	8 (47.1)
Disease progression	16 (55.2)	17 (40.5)	17 (41.5)	22 (64.7)	11 (40.7)	5 (33.3)	2 (11.8)
Noncompliance with study treatment	0	1 (2.4)	0	0	1 (3.7)	0	0
Physician decision	2 (6.9)	2 (4.8)	2 (4.9)	3 (8.8)	0	0	0
Patient request	5 (17.2)	10 (23.8)	4 (9.8)	2 (5.9)	3 (11.1)	5 (33.3)	6 (35.3)

Abbreviations: MM, multiple myeloma; WM, Waldenström macroglobulinemia.

therefore determined to be 300 mg/day for the 2/7 schedule and 240 mg/day for the 5/14 schedule. The most commonly observed treatment-emergent AEs in the phase Ib portion of the study were nausea, diarrhea, vomiting, fatigue, and constipation (Supplementary Table S2). Peripheral neuropathy and rash were infrequent, and no treatment-emergent grade ≥3 peripheral neuropathy was observed in the phase 1b portion of the study. Five patients (17.2%) with multiple myeloma or Waldenström macroglobulinemia on the 2/7 schedule discontinued treatment due to AEs, compared with 8 patients (19.0%) on the 5/14 schedule, respectively (Table 2). No patients in the phase Ib portion died within 30 days after receiving their last dose of oprozomib.

On the basis of MTD, efficacy, and safety data from the phase Ib portion of the study, patients in the phase II portion were initially treated on the 5/14 schedule at the MTD of 240 mg/day. In the phase II portion of the study, 2 patients with multiple myeloma who were treated in this cohort died on study due to gastrointestinal hemorrhage, possibly related to oprozomib toxicity (1 patient also died due to plasma cell myeloma in the context of disease progression). The study protocol was amended to address the gastrointestinal hemorrhage observed in the 2 patients, as well as the higher than desired gastrointestinal toxicity observed in the initial phase II cohorts on the 5/14, 240-mg/day schedule. Patients were subsequently enrolled in the 2/7 and 5/14 step-up dosing schedules (240/300 mg/day and 150/180 mg/day, respectively). All patients reported at least 1 AE of any grade. Rates of grade ≥3 AEs were 90.2% (multiple myeloma, 2/7 schedule, 240/300 mg/day), 64.7% (multiple myeloma, 5/14 schedule, 150/180 mg/day), 85.2% (multiple myeloma, 5/14 schedule, 240 mg/day), 53.3% (Waldenström macroglobulinemia, 2/7 schedule, 240/300 mg/day), and 47.1% (Waldenström macroglobulinemia, 5/14 schedule, 240 mg/day). Across all cohorts, the most common grade ≥3 AEs included diarrhea, anemia, thrombocytopenia, fatigue, nausea, and vomiting (Table 3). Rates of these grade ≥3 AEs were generally higher among patients with multiple myeloma in the 5/14, 240-mg/day schedule compared with the 2/7, 240/300-mg/day schedule; among patients with Waldenström macroglobulinemia, rates of these AEs were generally similar between the 2/7 and 5/14 dosing schedules. Among patients with multiple myeloma, rates of treatment discontinuation due to AEs were 39.0%, 11.8%, and 44.4% in the 2/7, 240/300-mg/day; 5/14, 150/180-mg/day; and 5/14, 240-mg/day cohorts, respectively. Among patients with Waldenström macroglobulinemia, rates of treatment discontinuation due to AEs were 13.3% and 47.1% on the 2/7 and 5/14 schedules, respectively. No deaths occurred on the 2/7 schedule or in the 5/14 step-up dosing cohorts ≤30 days after the date of the last dose. All patients received antiemetic medication; rates of antidiarrheal medication administration by cohort ranged from 35% to 93%.

Response

The data cutoff for the final analysis of this study was August 8, 2016. In phase Ib, 26 patients on the 2/7 schedule and 39 patients on the 5/14 schedule were eligible for response evaluation (Supplementary Table S3). On the 2/7 schedule, the ORRs for patients with multiple myeloma and Waldenström macroglobulinemia were 27.8% and 37.5%, respectively. On the 5/14 schedule, the ORRs for patients with multiple myeloma and Waldenström macroglobulinemia were 46.4% and 81.8%, respectively.

In phase II, among response-eligible patients with multiple myeloma, ORRs were 41.0%, 28.1%, and 25.0% in the 2/7, 240/300-mg/day ($n = 39$); 5/14, 150/180-mg/day ($n = 32$); and 5/14, 240-mg/day ($n = 24$) cohorts, respectively (Table 4). Among patients with multiple myeloma who were bortezomib-refractory, ORRs were 31.0% and 17.9% on the 2/7 ($n = 29$) and 5/14 ($n = 39$) schedules, respectively (Supplementary Table S4). Among patients with multiple myeloma who were carfilzomib-refractory, ORRs were 14.3% and 9.5% on the 2/7 ($n = 14$) and 5/14 ($n = 21$) schedules, respectively. For response-eligible patients with Waldenström macroglobulinemia, ORRs were 71.4% and 47.1% on the 2/7 ($n = 14$) and 5/14 ($n = 17$) schedules, respectively (Table 4). The ORR in 10 rituximab-refractory Waldenström macroglobulinemia patients on the 2/7 schedule was 70.0%; the ORR in 16 rituximab-refractory Waldenström macroglobulinemia patients on the 5/14 schedule was 62.5% (Supplementary Table S4). Among patients with multiple myeloma, Kaplan–Meier median PFS was 6.1 months in the 2/7, 240/300-mg/day schedule; 3.7 months in the 5/14, 150/180-mg/day schedule; and 3.8 months in the 5/14, 240-mg/day schedule (Fig. 2A). Among patients with Waldenström macroglobulinemia, Kaplan–Meier median PFS was 17.1 months in the 2/7, 240/300-mg/day schedule; and 21.9 months in the 5/14, 240-mg/day schedule (Fig. 2B).

Pharmacokinetics and pharmacodynamics

Oprozomib was rapidly absorbed following administration of capsule and tablet in patients with multiple myeloma and tablet in patients with Waldenström macroglobulinemia. Median t_{max} ranged from 0.4 to 2 hours for the capsule (Supplementary Table

Table 3. AEs of any grade occurring in ≥30% of patients in any cohort and grade ≥3 AEs occurring in ≥10% of patients in any cohort

	Phase Ib		Phase II										Total	
	MM or WM		MM						WM				WM + MM	
	5/14 schedule, 240 mg/day		2/7 schedule, 240/300 mg/day		5/14 schedule, 150/180 mg/day		5/14 schedule, 240 mg/day		2/7 schedule, 240/300 mg/day		5/14 schedule, 240 mg/day		5/14 schedule, 240 mg/day	
	(*n* = 8)		(*n* = 41)		(*n* = 34)		(*n* = 27)		(*n* = 15)		(*n* = 17)		(*n* = 52)	
AE, *n* (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Diarrhea	6 (75.0)	2 (25.0)	37 (90.2)	11 (26.8)	30 (88.2)	4 (11.8)	23 (85.2)	9 (33.3)	14 (93.3)	4 (26.7)	12 (70.6)	1 (5.9)	41 (78.8)	12 (23.1)
Nausea	8 (100.0)	2 (25.0)	35 (85.4)	3 (7.3)	27 (79.4)	0	25 (92.6)	10 (37.0)	15 (100)	1 (6.7)	14 (82.4)	1 (5.9)	47 (90.4)	13 (25.0)
Fatigue	4 (50.0)	1 (12.5)	27 (65.9)	8 (19.5)	13 (38.2)	3 (8.8)	16 (59.3)	4 (14.8)	11 (73.3)	0	9 (52.9)	0	29 (55.8)	5 (9.6)
Vomiting	6 (75.0)	1 (12.5)	24 (58.5)	1 (2.4)	18 (52.9)	0	23 (85.2)	10 (37.0)	12 (80.0)	1 (6.7)	8 (47.1)	1 (5.9)	37 (71.2)	12 (23.1)
Anemia	3 (37.5)	0	16 (39.0)	8 (19.5)	8 (23.5)	3 (8.8)	12 (44.4)	8 (29.6)	1 (6.7)	0	3 (17.6)	0	18 (34.6)	8 (15.4)
Abdominal pain	1 (12.5)	0	13 (31.7)	3 (7.3)	4 (11.8)	0	11 (40.7)	3 (11.1)	7 (46.7)	1 (6.7)	2 (11.8)	1 (5.9)	14 (26.9)	4 (7.7)
Acute kidney injury	0	0	4 (9.8)	2 (4.9)	1 (2.9)	0	4 (14.8)	3 (11.1)	1 (6.7)	1 (6.7)	1 (5.9)	0	5 (9.6)	3 (5.8)
Back pain	1 (12.5)	0	9 (22.0)	0	6 (17.6)	1 (2.9)	9 (33.3)	3 (11.1)	2 (13.3)	0	0	0	10 (19.2)	3 (5.8)
Dehydration	3 (37.5)	0	7 (17.1)	2 (4.9)	3 (8.8)	1 (2.9)	6 (22.2)	5 (18.5)	0	0	2 (11.8)	0	11 (21.2)	5 (9.6)
Hypophosphatemia	1 (12.5)	0	1 (2.4)	0	5 (14.7)	2 (5.9)	4 (14.8)	3 (11.1)	0	0	1 (5.9)	0	6 (11.5)	3 (5.8)
Leukopenia	0	0	2 (4.9)	0	2 (5.9)	0	5 (18.5)	4 (14.8)	0	0	1 (5.9)	0	6 (11.5)	4 (7.7)
Neutropenia	2 (25.0)	0	5 (12.2)	2 (4.9)	3 (8.8)	0	6 (22.2)	4 (14.8)	0	0	0	0	8 (15.4)	4 (7.7)
Cough	1 (12.5)	0	8 (19.5)	0	9 (26.5)	0	7 (25.9)	0	6 (40.0)	0	1 (5.9)	0	9 (17.3)	0
Insomnia	1 (12.5)	0	4 (9.8)	0	3 (8.8)	0	7 (25.9)	0	5 (33.3)	0	2 (11.8)	0	10 (19.2)	0
Abdominal distension	1 (12.5)	0	12 (29.3)	0	11 (32.4)	0	2 (7.4)	0	8 (53.3)	0	5 (29.4)	0	8 (15.4)	0
Blood creatinine increased	3 (37.5)	0	9 (22.0)	3 (7.3)	9 (26.5)	0	6 (22.2)	0	2 (13.3)	0	1 (5.9)	0	10 (19.2)	0
Constipation	3 (37.5)	0	11 (26.8)	0	15 (44.1)	0	9 (33.3)	0	8 (53.3)	0	11 (64.7)	0	23 (44.2)	0
Headache	1 (12.5)	0	10 (24.4)	0	3 (8.8)	1 (2.9)	4 (14.8)	0	6 (40.0)	1 (6.7)	3 (17.6)	0	8 (15.4)	0
Thrombocytopenia	3 (37.5)	1 (12.5)	10 (24.4)	5 (12.2)	4 (11.8)	1 (2.9)	10 (37.0)	9 (33.3)	0	0	0	0	13 (25.0)	10 (19.2)
Pyrexia	1 (12.5)	0	6 (14.6)	0	5 (14.7)	0	3 (11.1)	0	6 (40.0)	0	3 (17.6)	0	7 (13.5)	0
Decreased appetite	3 (37.5)	1 (12.5)	9 (22.0)	1 (2.4)	8 (23.5)	0	17 (63.0)	0	7 (46.7)	0	7 (41.2)	0	27 (51.9)	1 (1.9)
Dyspepsia	1 (12.5)	0	8 (19.5)	0	8 (23.5)	0	3 (11.1)	0	6 (40.0)	0	2 (11.8)	0	6 (11.5)	0
Gastroesophageal reflux disease	1 (12.5)	0	6 (14.6)	0	1 (2.9)	0	6 (22.2)	0	5 (33.3)	0	3 (17.6)	0	10 (19.2)	0
Platelet count decreased	0	0	5 (12.2)	5 (12.2)	4 (11.8)	3 (8.8)	1 (3.7)	1 (3.7)	2 (13.3)	1 (6.7)	0	0	1 (1.9)	1 (1.9)
Pneumonia	2 (25.0)	0	3 (7.3)	2 (4.9)	1 (2.9)	1 (2.9)	2 (7.4)	0	2 (13.3)	2 (13.3)	0	0	4 (7.7)	0
Sepsis	0	0	1 (2.4)	1 (2.4)	0	0	0	0	2 (13.3)	2 (13.3)	0	0	0	0
Upper abdominal pain	2 (25.0)	0	8 (19.5)	0	3 (8.8)	0	6 (22.2)	0	4 (26.7)	0	1 (5.9)	0	9 (17.3)	0
Nasal congestion	0	0	0	0	2 (5.9)	0	0	0	4 (26.7)	0	1 (5.9)	0	1 (1.9)	0
Hypertension	1 (12.5)	1 (12.5)	6 (14.6)	3 (7.3)	4 (11.8)	2 (5.9)	1 (3.7)	1 (3.7)	0	0	1 (5.9)	1 (5.9)	3 (5.8)	3 (5.8)
Influenza	1 (12.5)	1 (12.5)	2 (14.9)	0	1 (2.9)	0	0	0	1 (6.7)	1 (6.7)	1 (5.9)	0	2 (3.8)	1 (1.9)
Syncope	1 (12.5)	1 (12.5)	2 (14.9)	1 (2.4)	1 (2.9)	1 (2.9)	0	0	0	0	1 (5.9)	1 (5.9)	2 (3.8)	2 (3.8)
Tumor lysis syndrome	1 (12.5)	1 (12.5)	1 (2.4)	1 (2.4)	0	0	0	0	0	0	0	0	1 (1.9)	1 (1.9)
Urinary tract infection	1 (12.5)	1 (12.5)	4 (9.8)	2 (4.9)	3 (8.8)	0	2 (7.4)	2 (7.4)	1 (6.7)	0	1 (5.9)	0	4 (7.7)	3 (5.8)

Abbreviations: MM, multiple myeloma; WM, Waldenström macroglobulinemia.

Table 4. Best overall response in the phase II portion of the study (response-eligible population)

	MM[a]			WM[a]	
Outcome	**2/7 schedule, 240/300 mg/day (*n* = 39)**	**5/14 schedule, 150/180 mg/day (*n* = 32)**	**5/14 schedule, 240 mg/day (*n* = 24)**	**2/7 schedule, 240/300 mg/day (*n* = 14)**	**5/14 schedule, 240 mg/day (*n* = 17)**
Best overall response, *n* (%)					
Very good partial response	5 (12.8)	3 (9.4)	3 (12.5)	3 (21.4)	0
Partial response	11 (28.2)	6 (18.8)	3 (12.5)	4 (28.6)	5 (29.4)
Minimal response	4 (10.3)	1 (3.1)	2 (8.3)	3 (21.4)	3 (17.6)
SD	8 (20.5)	11 (34.4)	9 (37.5)	4 (28.6)	8 (47.1)
Progressive disease	7 (17.9)	11 (34.4)	2 (8.3)	0	0
Not evaluable	1 (2.6)	0	3 (12.5)	0	1 (5.9)
Off study prior to response assessment	0	0	0	0	0
Missing	3 (7.7)	0	2 (8.3)	0	0
ORR, % (95% CI)	41.0 (25.6–57.9)	28.1 (13.7–46.7)	25.0 (9.8–46.7)	71.4 (41.9–91.6)	47.1 (23.0–72.2)
Median duration of response, months	10.2	12.5	5.6	NE	20.7
Median time to response, months	1.9	1.9	1.0	1.0	1.2
CBR, % (95% CI)	51.3 (34.8–67.6)	31.3 (16.1–50.0)	33.3 (15.6–55.3)	—	—
MRR, % (95% CI)	—	—	—	50.0 (23.0–77.0)	29.4 (10.3–56.0)
Median duration of SD or better, months (95% CI)	7.7 (4.2–13.4)	5.1 (3.1–13.7)	5.6 (2.6–NE)	17.1 (6.0–NE)	21.9 (13.8–NE)

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; MM, multiple myeloma; MRR, major response rate; NE, not estimable; SD, stable disease; WM, Waldenström macroglobulinemia.

[a]For duration of response, time to response, and ORR, response was defined as a partial response or better (MM) or as a minimal response or better (WM). CBR for MM was defined as minimal response or better. MRR for WM was defined as partial response or better.

S5) and 0.8 to 2 hours for the tablet in patients with multiple myeloma, and 0.5 to 2 hours for the tablet in patients with Waldenström macroglobulinemia (Supplementary Table S6). Oprozomib was rapidly eliminated with a mean terminal elimination half-life of 0.52 to 1.8 hours after tablet administration for patients with multiple myeloma and 0.67 to 2.5 hours after tablet administration for patients with Waldenström macroglobulinemia (Supplementary Table S6). Half-life was not well characterized for capsules in patients with multiple myeloma, with terminal elimination half-life of 5.2 hours observed in a single patient (Supplementary Table S5).

There was, in general, a dose-related increase in oprozomib exposure (as assessed by AUC) following administration of oprozomib in capsules twice daily (separated by 4–6 hours) to patients with multiple myeloma over the total daily dose range of 120 to 210 mg (Supplementary Table S5). Furthermore, a dose-related increase in oprozomib exposure (as assessed by C_{max} and AUC_{last}) was observed following administration of oprozomib tablets once daily over the dose range of 150 to 330 mg in patients with multiple myeloma and over the dose range of 150 to 300 mg in patients with Waldenström macroglobulinemia (Supplementary Table S6). Lower exposures were observed for the 330 mg dose level compared with the 300 mg dose level for patients with Waldenström macroglobulinemia, although only a small number of subjects were evaluated (2 subjects for each dose level). High intersubject variability was observed by percent of coefficient of variation (CV%) up to 130% for oprozomib in capsules and up to 157% for oprozomib tablets across the cohorts for AUC_{last} and C_{max}. These results should be interpreted with caution considering the observed intersubject variability and small number of subjects evaluated.

Potent proteasome inhibition was observed in whole blood 8 hours after administration of the first dose of oprozomib tablets in the phase Ib portion of the study (Supplementary Fig. S2A). At the MTD on both the 2/7 and 5/14 schedules, proteasome inhibition of approximately $\geq$70% was observed at 4 hours postdose (Supplementary Fig. S2B). Data obtained from the evaluation of the pharmacodynamics of the oprozomib split-dose PIC formulation are presented in Supplementary Fig. S3.

Discussion

In this phase Ib/II study, the first to evaluate safety and efficacy outcomes of single-agent oprozomib in patients with multiple myeloma and Waldenström macroglobulinemia, different formulations and dosing schedules of oprozomib were evaluated. In the phase Ib portion, the MTD was determined to be 300 mg/day for the 2/7 schedule and 240 mg/day for the 5/14 schedule. However, 2 patients treated at the 5/14 schedule MTD in the phase II portion died due to gastrointestinal hemorrhage, and subsequent patients were enrolled on step-up dosing schemes. The step-up dosing regimen addressed the higher than desired gastrointestinal toxicity and discontinuation rates observed in the early phase II cohorts in which patients were administered oprozomib 240 mg/day on the 5/14 schedule. In our study, step-up dosing appeared to be better tolerated than continuous dosing, possibly because step-up dosing allowed oprozomib levels to rise gradually. The most common AEs of any grade observed with single-agent oprozomib were gastrointestinal toxicities. Steps were taken during the study to improve the gastrointestinal tolerability of oprozomib, including protocol amendments that required the use of concomitant antidiarrheal medication and premedication with a 5-hydroxytryptamine-3 inhibitor. Fatigue and hematologic toxicities, including anemia and thrombocytopenia, were also observed in $\geq$30% of patients. When comparing the efficacy and safety between the different treatment dosing schedules in phase II, we found that ORRs were higher in the 2/7 schedule than in the 5/14 schedule in both multiple myeloma and Waldenström macroglobulinemia patients. In phase II, rates of grade $\geq$3 AEs were lower in the 5/14, 150/180-mg/day schedule than in the 2/7, 240/300-mg/day and the 5/14, 150/180-mg/day schedules. In patients with Waldenström macroglobulinemia, rates of grade $\geq$3 AEs were similar between the 2/7 and 5/14 schedules.

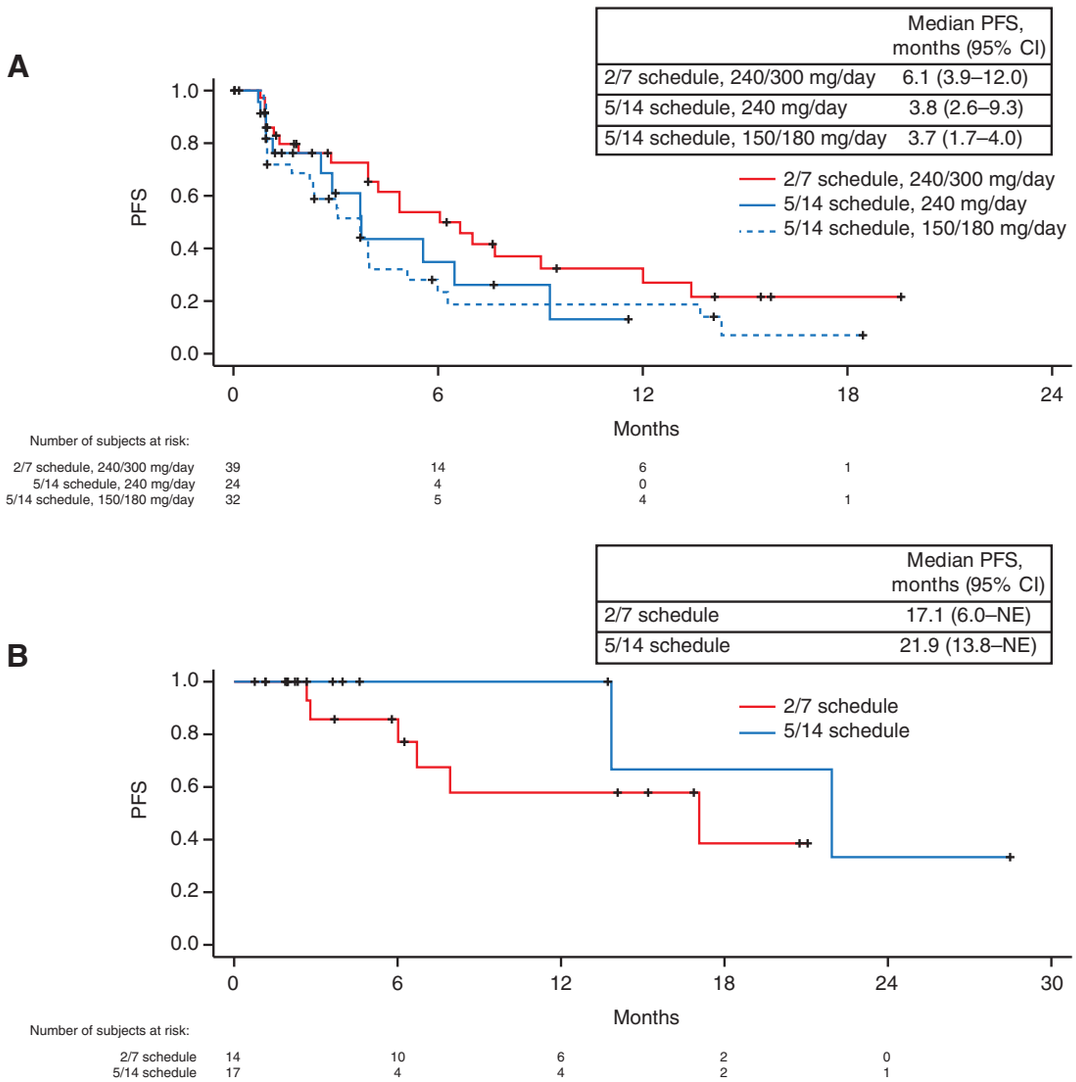


Figure 2.
Kaplan–Meier PFS curves for patients with multiple myeloma (**A**) and Waldenström macroglobulinemia (**B**). CI, confidence interval; NE, not estimable.

The pharmacokinetic and pharmacodynamic profile of oprozomib had previously been examined in a phase I study of patients with solid tumors, which demonstrated that oprozomib had oral bioavailability and exhibited dose-dependent inhibition of the proteasome (17). In this study, although high interpatient variability was observed, pharmacokinetic and pharmacodynamic parameters were generally similar to those observed with carfilzomib, with more patients achieving approximately 80% proteasome inhibition at 4 hours postdose compared with 1 hour postdose when single-agent oprozomib was administered at the MTD.

Despite the similarities in pharmacokinetics/pharmacodynamics between oprozomib and carfilzomib, the AE profiles of these agents differ to some extent. Carfilzomib has been associated with cardiac and renal events in phase II and III studies (8, 9, 21). In our study, the most common grade ≥3 AEs associated with oprozomib were gastrointestinal and hematologic in nature, and cardiac failure or hypertension were infrequent. The differences in cardiac toxicity between oprozomib and carfilzomib could be related to variations in C_{max}, while differences in gastrointestinal toxicity could be related to the route of administration (oral vs. intravenous). In two phase I studies of single-agent oral ixazomib in RR multiple myeloma, the most common treatment-related AEs were similar to those observed with oprozomib in our study, and included thrombocytopenia, diarrhea, nausea, and vomiting (22, 23). However, the gastrointestinal AE rates for ixazomib were lower than the rates seen in our study with oprozomib (22, 23), underscoring the need for an improved oprozomib formulation with reduced gastrointestinal toxicity.

The study underwent several changes resulting from protocol amendments, including changes to the formulation of oprozomib. Initially, enrolled patients received oprozomib twice-daily as a split-dose PIC. Because of gastrointestinal toxicities

observed in patients receiving the PIC formulation, the protocol was amended to administer oprozomib as a once-daily modified-release tablet. Pharmacokinetic and pharmacodynamic properties were found to be similar between the split-dose PIC and modified-release tablet formulations in preclinical models (24) and in preliminary results from the current study (25). We also note that 2 patients with chronic lymphocytic leukemia and 1 each with follicular and mantle cell lymphoma were enrolled into the phase I portion of this study, but due to the small sample sizes of these cohorts they have not been characterized here.

Oprozomib showed promising antitumor activity in patients with either multiple myeloma or Waldenström macroglobulinemia. With the caveat that cross-trial comparisons should be interpreted with caution, the ORRs (defined as partial response or better) observed in the phase II portion of this study for patients with multiple myeloma (25.0%–41.0%) were similar to or higher than that of phase I–III trials of other PIs administered as single agents in the relapsed setting (2, 3, 22, 23, 26). In two phase I studies of ixazomib in patients with RR multiple myeloma, ORR was 15% to 18% (22, 23), and a phase II study of intravenously administered carfilzomib in RR multiple myeloma patients demonstrated an ORR of 23.7% (26). For intravenously administered bortezomib in RR multiple myeloma patients, the ORR was 27% in a phase II trial (2) and 38% in a phase III trial (3). For Waldenström macroglobulinemia, the only currently approved treatment is the Bruton tyrosine kinase inhibitor ibrutinib. In the phase II study that led to ibrutinib approval, the ORR was 90.5% and the major response rate (partial response or better) was 73% (27). In our study, the phase II ORRs for patients with Waldenström macroglobulinemia were encouraging, albeit somewhat lower (71.4% and 47.1% on the 2/7 and 5/14 schedules, respectively) than those of ibrutinib, possibly because treatment discontinuation rates were higher in our study than in the ibrutinib study (27). Higher ORRs with oprozomib are likely to be observed in future studies with larger Waldenström macroglobulinemia patient populations, and by improving drug formulations to prevent AE-related discontinuations.

In conclusion, this study shows as proof of principle substantial single-agent oprozomib activity in patients with relapsed multiple myeloma or Waldenström macroglobulinemia, with durable responses overall and responses observed in those refractory to bortezomib or carfilzomib. Despite the efficacy observed with oprozomib as a single agent, there are challenges associated with tolerability. In particular, gastrointestinal events (primarily diarrhea) were among the most common grade $\geq$3 AEs with single-agent oprozomib. Because of these tolerability limitations, the oprozomib modified-release tablet formulation used in this study is not planned for future studies; rather, oprozomib safety and efficacy are currently being evaluated with immediate-release and gastroretentive tablet formulations and optimized schedule and dosing administration. These studies aim for at least comparable activity and improved single-agent tolerability, particularly gastrointestinal tolerability. For example, in the phase Ib study INTREPID-1 (NCT02939183), the two new formulations of oprozomib plus pomalidomide and dexamethasone are being evaluated in patients with relapsed refractory multiple myeloma. In addition, steroids (e.g., dexamethasone) at doses higher than recommended in this protocol have been shown to reduce gastrointestinal toxicities (28), justifying further development of oprozomib combinations containing dexamethasone. Consequently, other studies of oprozomib and dexamethasone with or without other agents are ongoing, including a phase Ib/II study of oprozomib and dexamethasone plus lenalidomide or oral cyclophosphamide in patients with newly diagnosed multiple myeloma (NCT01881789), a phase Ib/II study of oprozomib and dexamethasone in patients with relapsed and/or refractory multiple myeloma (NCT01832727; ref. 29), and a phase Ib study of oprozomib with pomalidomide and dexamethasone in patients with primary refractory or relapsed and refractory multiple myeloma (NCT01999335).

Disclosure of Potential Conflicts of Interest

R. Vij is a consultant/advisory board member for Amgen, Celgene, Bristol-Myers Squibb, Takeda, Janssen, Karypopharm, and Sanofi and reports receiving commercial research grants from Takeda, Celgene, and Bristol-Myers Squibb. D. Siegel reports receiving speakers bureau honoraria from and is a consultant/advisory board member for Amgen. J. Kaufman is a consultant/advisory board member for Celgene, Takeda, Bristol-Myers Squibb, Janssen, Karyopharm, TG Therapeutics, and Incyte. N. Raje is a consultant/advisory board member for Amgen, Celgene, Janssen, Takeda, and Bristol-Myers Squibb. A. Jakubowiak is a consultant/advisory board member for Amgen, Celgene, AbbVie, Bristol-Myers Squibb, Janssen, Juno, Karyopharm, SkylindeDX, and Takeda. M.R. Savona has ownership interest (including patents) in Karyopharm, is a consultant/advisory board member for Celgene, Karyopharm, Incyte, TG Therapeutics, Takeda, Amgen, and Astex, and reports receiving commercial research grants from Incyte, Takeda, TG Therapeutics, Sunesis, and Astex. J.G. Berdeja is a consultant/advisory board member for Takeda, Bristol-Myers Squibb, Karyopharm, CRISPR Therapeutics, Kite Pharma, and Servier and reports receiving commercial research grants from AbbVie, Amgen, Bluebird, Bristol-Myers Squibb, Celgene, Genentech, Glenmark, Janssen, Novartis, Poseida, Sanofi, Takeda, and Teva. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: I.M. Ghobrial, D. Siegel, A. Badros, M.R. Savona, M. Obreja

Development of methodology: I.M. Ghobrial, D. Siegel, M. Obreja

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): I.M. Ghobrial, R. Vij, D. Siegel, A. Badros, J. Kaufman, N. Raje, A. Jakubowiak, M.R. Savona, J.G. Berdeja

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I.M. Ghobrial, R. Vij, D. Siegel, A. Badros, J. Kaufman, A. Jakubowiak, M.R. Savona, M. Obreja, J.G. Berdeja

Writing, review, and/or revision of the manuscript: I.M. Ghobrial, R. Vij, D. Siegel, A. Badros, J. Kaufman, N. Raje, A. Jakubowiak, M.R. Savona, M. Obreja, J.G. Berdeja

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Obreja

Study supervision: I.M. Ghobrial, A. Badros, M.R. Savona, M. Obreja

Acknowledgments

The authors wish to thank all the patients, families, caregivers, research nurses, study coordinators, and support staff who contributed to this study. Medical writing and editorial assistance was provided by Andrew Gomes and Sachi Yim of BlueMomentum, an Ashfield Company, part of UDG Healthcare PLC, and funded by Amgen Inc. This study was supported by Amgen Inc.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 27, 2018; revised February 7, 2019; accepted May 14, 2019; published first May 29, 2019.

References

1. San-Miguel JF, Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, et al. Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study. Leukemia 2008;22: 842–49.
2. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609–17.
3. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487–98.
4. Kouroukis TC, Baldassarre FG, Haynes AE, Imrie K, Reece DE, Cheung MC. Bortezomib in multiple myeloma: systematic review and clinical considerations. Curr Oncol 2014;21:e573–e603.
5. Millenium Pharmaceuticals, Inc. Velcade full prescribing information. 2017. Available from: http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf.
6. Mu SD, Ai LS, Qin Y, Hu Y. Subcutaneous versus intravenous bortezomib administration for multiple myeloma patients: a meta-analysis. Curr Med Sci 2018;38:43–50.
7. Amgen Inc. Kyprolis (carfilzomib) for Injection full prescribing information. 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf.
8. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol 2016; 17:27–38.
9. Siegel D, Martin T, Nooka A, Harvey RD, Vij R, Niesvizky R, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica 2013;98:1753–61.
10. Moreau P, Mateos M-V, Berenson JR, Weisel K, Lazzaro A, Song K, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. Lancet Oncol 2018;19:953–64.
11. Takeda Pharmaceutical Company Limited. Ninlaro (ixazomib) full prescribing information. 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf.
12. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;374:1621–34.
13. Mateos MV, Masszi T, Grzasko N, Hansson M, Sandhu I, Pour L, et al. Impact of prior therapy on the efficacy and safety of oral ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1. Haematologica 2017;102:1767–75.
14. Zhou HJ, Aujay MA, Bennett MK, Dajee M, Demo SD, Fang Y, et al. Design and synthesis of an orally bioavailable and selective peptide epoxyketone proteasome inhibitor (PR-047). J Med Chem 2009;52:3028–38.
15. Chauhan D, Singh AV, Aujay M, Kirk CJ, Bandi M, Ciccarelli B, et al. A novel orally active proteasome inhibitor ONX 0912 triggers in vitro and in vivo cytotoxicity in multiple myeloma. Blood 2010;116:4906–15.
16. Roccaro AM, Sacco A, Aujay M, Ngo HT, Azab AK, Azab F, et al. Selective inhibition of chymotrypsin-like activity of the immunoproteasome and constitutive proteasome in Waldenstrom macroglobulinemia. Blood 2010;115:4051–60.
17. Infante JR, Mendelson DS, Burris HA III, Bendell JC, Tolcher AW, Gordon MS, et al. A first-in-human dose-escalation study of the oral proteasome inhibitor oprozomib in patients with advanced solid tumors. Invest New Drugs 2016;34:216–24.
18. Durie BGM, Harousseau J-L, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–73.
19. Owen RG, Kyle RA, Stone MJ, Rawstron AC, Leblond V, Merlini G, et al. VIth International Workshop on Waldenstrom macroglobulinaemia. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. Br J Haematol 2013;160:171–6.
20. Lee SJ, Levitsky K, Parlati F, Bennett MK, Arastu-Kapur S, Kellerman L, et al. Clinical activity of carfilzomib correlates with inhibition of multiple proteasome subunits: application of a novel pharmacodynamic assay. Br J Haematol 2016;173:884–95.
21. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, S?pička I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142–52.
22. Richardson PG, Baz R, Wang M, Jakubowiak AJ, Laubach JP, Harvey RD, et al. Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. Blood 2014;124: 1038–46.
23. Kumar SK, Bensinger WI, Zimmerman TM, Reeder CB, Berenson JR, Berg D, et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. Blood 2014;124:1047–55.
24. Teague J, Wong H, Bejugam N, Kidney D, Muchamuel T, Anderl J, et al. Development of modified release tablets for oprozomib: mitigation of GI toxicity without compromising oral absorption. In: Proceedings of the 2014 American Association of Pharmaceutical Scientists Annual Meeting; 2014 Nov 2–6; San Diego, CA. Arlington (VA): AAPS. Poster nr W4256.
25. Siegel DS, Berdeja J, Vij R, Kaufman J, Ghobrial I, Badros A, et al. Oprozomib (OPZ) treatment in patients (pts) with hematologic malignancies: updated results from a phase 1b/2 trial. In: Proceedings of the 14th International Myeloma Workshop; 2013 Apr 3–7; Kyoto, Japan. Rochester (MN): International Myeloma Society; 2013. Poster nr P-225.
26. Siegel D, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood 2012;120:2817–25.
27. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med 2015; 372:1430–40.
28. Jagannath S, Richardson RG, Barlogie B, Berenson JR, Singhal S, Irwin D, 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 2006;91:929–34.
29. Prada CP, Shain KH, Voorhees P, Gabrail N, Abidi M, Zonder J, et al. Oprozomib (OPZ) and dexamethasone (DEX) in patients (Pts) with relapsed and/or refractory multiple myeloma (RRMM): updated results from a phase 1b/2, multicenter, open-label study. Clin Lymphoma Myeloma Leuk 2015;15(Suppl 3):e273(abstract PO-338).