Results of the Dose-Escalation Portion of a Phase 1/2 Study (CHAMPION-1) Investigating Weekly Carfilzomib in Combination With Dexamethasone for Patients With Relapsed or Refractory Multiple Myeloma

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8594

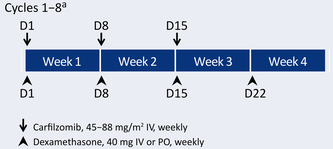
INTRODUCTION

- Carfilzomib is a selective proteasome inhibitor approved in the United States for the treatment of relapsed and refractory multiple myeloma (MM)[1,2]
- The approved dose and schedule for single-agent carfilzomib is 20/27 mg/m^2 (20 mg/m^2 administered in cycle 1, dose escalation to a target dose of 27 mg/m^2 thereafter) administered intravenously (IV) over 2 to 10 minutes on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle
- Using the same dosing schedule, 20/56 mg/m^2 carfilzomib (20 mg/m^2 on days 1 and 2 of cycle 1, 56 mg/m^2 thereafter) administered IV over 30 minutes has been found to be well tolerated as a single agent or in combination with dexamethasone (40 mg/week; 20 mg on days 1, 2, 8, 9, 15, and 16), with an overall response rate (ORR) of 50% for patients with relapsed and/or refractory MM (median of 4 prior chemotherapies) who received single-agent carfilzomib and 55% for patients who received carfilzomib-dexamethasone[3]
  - Carfilzomib with dexamethasone is being tested in the randomized phase 3 study ENDEAVOR (NCT01568866)
- To extend the findings from treatment with higher doses of carfilzomib infused over 30 minutes twice weekly, this multicenter, single-arm, phase 1/2 study (CHAMPION-1; NCT01677858) is evaluating the safety and efficacy of once-weekly carfilzomib with dexamethasone (40 mg) for patients with relapsed or refractory MM
  - Preliminary results from the phase 1 dose-escalation portion of the study were presented at the 2013 ASH Annual Meeting;[4] updated results are presented herein

PATIENTS AND METHODS

- Patients with relapsed or refractory MM who received 1 to 3 prior regimens were eligible for enrollment
- Patients were treated with carfilzomib as a 30-minute IV infusion on days 1, 8, and 15 of each 28-day cycle in a standard 3+3 dose-escalation scheme **(Figure 1)**
- All patients received carfilzomib (20 mg/m^2) on day 1 of cycle 1; subsequent doses started at 45 mg/m^2 in the first cohort and were escalated to 56, 70, or 88 mg/m^2 in successive cohorts until the maximum tolerated dose (MTD) was determined
  - An expansion cohort of an additional 9 patients was also to be enrolled to confirm the MTD before moving to the phase 2 portion of the study (ie, 15 patients at the MTD)
- Patients received 40 mg dexamethasone (IV or perorally administered) on days 1, 8, 15, and 22 of cycles 1 through 8. Administration of dexamethasone on day 22 was omitted from cycle 9 and beyond

Figure 1. Dosing Schedule (28-Day Cycle)



Cohort	Carfilzomib[b] mg/m^2	Dexamethasone mg
1	45	40
2	56	40
3	70	40
4	88	40

D, day; IV, intravenously; PO, perorally.
[a]During cycles 9 and beyond, dexamethasone was administered (IV/PO) on D1, D8, and D15.
[b]All patients received 20 mg/m^2 carfilzomib on D1 of cycle 1; subsequent doses were escalated to the indicated levels.

- The primary objective of the phase 1 portion of the study was to determine the MTD of weekly carfilzomib in combination with dexamethasone
- Secondary objectives included assessment of safety and tolerability, and defining the pharmacokinetic (PK) parameters of weekly carfilzomib
- Response was assessed according to the guidelines of the International Myeloma Working Group, with the addition of minimal response as defined by criteria from the European Blood and Marrow Transplantation Group[5,6]
- PK assessments included estimation of the area under the plasma concentration–time curve (AUC), maximum concentration (C_{max}), and terminal half-life
  - Blood samples were collected for PK analysis from patients in the 70-mg/m^2 (n=6) and 88-mg/m^2 (n=6) cohorts on days 1 and 15 of cycle 1 at the following time points: predose, 5, 15, and 30 minutes following the start of infusion, and 5, 15, and 30 minutes, and 1, 2, and 4 hours after the end of infusion
    - PK analysis for 20 mg/m^2 dosing was derived from day 1, cycle 1 blood samples

RESULTS

Enrollment and Patient Demographics

- The data cutoff date for this analysis was May 5, 2014
- Twenty-seven patients were enrolled in the phase 1 portion of the study
- Patient demographics and disease characteristics are shown in **Table 1**
  - Patients had received a median of 1 prior regimen, including prior bortezomib treatment in 85% of patients
    - Fifty-six percent of patients received 1 prior regimen, 41% received 2 prior regimens, and 4% received 3 prior regimens
    - The majority of patients (63%) were refractory to bortezomib
  - Thirteen patients (48%) had an ongoing medical history of peripheral neuropathy at study entry
- During dose escalation, the 45-mg/m^2 and 56-mg/m^2 dosing cohorts enrolled 3 patients each; the 70-mg/m^2 and 88-mg/m^2 dosing cohorts enrolled 6 patients each
  - Per protocol, the 70-mg/m^2 cohort was later expanded to include an additional 9 patients, for a total of 15 patients
  - Median treatment duration was 8.3 months (range, 0–20) in the overall population; 13 patients (48%) are still receiving treatment

Table 1. Baseline Characteristics

	Overall (N=27)
Male sex, n (%)	15 (56)
Age, years, median (range)	64 (43–84)
ISS stage at screening, n (%)	
I	17 (63)
II	6 (22)
III	4 (15)
ECOG performance status, n (%)	
0	12 (44)
1	15 (56)
Years since diagnosis, median (range)	3.1 (0.2–19.4)
Prior regimens, n, median (range)	1 (1–3)
Prior drugs, n, median (range)	4 (1–10)
Prior bortezomib, n (%)	23 (85)
Prior lenalidomide, n (%)	8 (30)

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.

Dose-Limiting Toxicities (DLTs) and MTD

- During dose-escalation, no DLTs were reported in the 45-mg/m^2, 56-mg/m^2, or 70-mg/m^2 cohorts
- At a carfilzomib dose of 88 mg/m^2, 2 DLTs were observed: grade 3 dyspnea (days 9–11) and grade 3 vomiting (day 15)
- Per protocol, an expansion cohort of 9 patients was enrolled at the next lowest dose (70 mg/m^2). There was 1 DLT in the 70-mg/m^2 expansion cohort: grade 3 dyspnea (days 16–18)
- The MTD of weekly carfilzomib in combination with weekly dexamethasone (40 mg) was 70 mg/m^2

Summary of Treatment-Emergent Adverse Events (AEs)

- All 27 patients were evaluable for safety **(Table 2)**

Table 2. Treatment-Emergent AEs Reported in ≥25% of Patients, Any Grade

	Dose-escalation cohorts				Dose-expansion cohort	
AE, n (%)	45 mg/m^2 (n=3)	56 mg/m^2 (n=3)	70 mg/m^2 (n=6)	88 mg/m^2 (n=6)	70 mg/m^2 (n=9)	Overall (N=27)
Hematologic AE						
Anemia	2 (67)	2 (67)	2 (33)	2 (33)	2 (22)	10 (37)
Decreased hematocrit level	2 (67)	2 (67)	2 (33)	3 (50)	1 (11)	10 (37)
Decreased red blood cell count	1 (33)	1 (33)	2 (33)	3 (50)	0	7 (26)
Nonhematologic AE						
Fatigue	3 (100)	2 (67)	3 (50)	3 (50)	3 (33)	14 (52)
Upper respiratory tract infection	1 (33)	2 (67)	5 (83)	2 (33)	4 (44)	14 (52)
Insomnia	2 (67)	1 (33)	2 (33)	5 (83)	2 (22)	12 (44)
Headache	0	2 (67)	3 (50)	4 (67)	2 (22)	11 (41)
Diarrhea	2 (67)	0	2 (33)	2 (33)	5 (56)	11 (41)
Nausea	0	1 (33)	2 (33)	3 (50)	5 (56)	11 (41)
Pyrexia	0	0	2 (33)	3 (50)	4 (44)	9 (33)
Constipation	1 (33)	1 (33)	2 (33)	1 (17)	3 (33)	8 (30)
Dyspnea	1 (33)	0	1 (17)	3 (50)	2 (22)	7 (26)
Back pain	2 (67)	0	2 (33)	0	3 (33)	7 (26)
Cough	0	0	4 (67)	2 (33)	1 (11)	7 (26)
Muscle spasms	0	0	3 (50)	3 (50)	1 (11)	7 (26)

AE, adverse event.

Table 3. Grade ≥3 Treatment-Emergent AEs Occurring in ≥2 patients

	Dose-escalation cohorts				Dose-expansion cohort	
AE, n (%)	45 mg/m^2 (n=3)	56 mg/m^2 (n=3)	70 mg/m^2 (n=6)	88 mg/m^2 (n=6)	70 mg/m^2 (n=9)	Overall (N=27)
Hematologic AE						
Thrombocytopenia	0	0	1 (17)	0	1 (11)	2 (7)
Nonhematologic AE						
Increased blood creatinine	1 (33)	0	1 (17)	0	0	2 (7)
Dyspnea	0	0	0	1 (17)	1 (11)	2 (7)
Upper respiratory tract infection	0	1 (33)	0	1 (17)	0	2 (7)
Back pain	0	0	1 (17)	0	1 (11)	2 (7)

AE, adverse event.

- Peripheral neuropathy was reported in 4 patients (grade 1, n=3; grade 2, n=1); peripheral sensory neuropathy was reported in 1 patient (grade 1)
- Additional Grade ≥3 AEs experienced by patients were neutropenia, hyperglycemia, decreased blood sodium, cellulitis, fatigue, headache, decreased blood potassium, muscular weakness, onychomycosis, pneumonia, maculopapular rash, urinary tract infection, vomiting, cataract, chronic obstructive pulmonary disease, pain in extremity, and spinal cord compression (n=1 each)

Treatment Discontinuations and Dose Modifications

- Fourteen patients discontinued treatment for the following reasons: AEs of increased blood creatinine (n=1; 70 mg/m^2), general weakness (n=1; 70 mg/m^2), headache (n=1; 88 mg/m^2), upper respiratory tract infection (n=1; 88 mg/m^2) and dyspnea (n=1; 88 mg/m^2); progressive disease (n=7), physician decision (n=1), and withdrawal of consent (n=1)
- Five of 6 patients had 1 or more carfilzomib dose reductions from 88 mg/m^2. Initial dose reductions to 70 mg/m^2 were due to an AE in 1 patient; a DLT in 1 patient; and were per protocol in 3 patients due to the 2 DLTs in the 88-mg/m^2 cohort
  - In the 45-mg/m^2, 56-mg/m^2, and 70-mg/m^2 dose escalation cohorts, no patients had a dose reduction
- Two of 9 patients in the 70-mg/m^2 expansion cohort had dose reductions due to AEs

Summary of Serious AEs

- Seven serious treatment-emergent AEs were reported. One patient had 2 serious treatment-emergent AEs (grade 3 increased blood creatinine and grade 4 hyponatremia), 1 patient had grade 3 pneumonia, 1 patient had grade 3 dyspnea, 1 patient had grade 3 rupturing appendicitis, 1 patient had grade 3 atrial fibrillation, and 1 patient had grade 3 chronic obstructive pulmonary disease
  - The grade 3 dyspnea event occurred in a patient receiving 88 mg/m^2 carfilzomib and was considered to be related to carfilzomib treatment; all other serious AEs were determined to be unrelated to carfilzomib or dexamethasone treatment
- No deaths were reported on treatment or within 30 days of treatment discontinuation

Pharmacokinetics

- PK analysis from patients who received 20/70 mg/m^2 or 20/88 mg/m^2 of carfilzomib showed a dose-proportional increase in mean C_{max} and AUC for 20 mg/m^2 to 88 mg/m^2, as shown by the similar dose-normalized values for C_{max} and AUC **(Table 4)**
- For the dosing range of 20 mg/m^2 to 88 mg/m^2, the mean terminal half-life of weekly carfilzomib was approximately 0.8 h
- Treatment with the 70-mg/m^2 weekly carfilzomib dose regimen resulted in lower C_{max} levels compared with those observed with the approved dose regimen of 20/27 mg/m^2 of carfilzomib twice a week (2640 ng/mL vs 4232 ng/mL, respectively)[1,7]

Table 4. Carfilzomib PK Parameters

		Terminal half-life, h		C_{max}, ng/mL		C_{max}/dose, (ng/mL)/(mg/m^2)	$AUC_{0\ last}$, h•ng/mL		AUC/dose, (h•ng/mL)/(mg/m^2)
Dose (mg/m^2)	n	Mean	%CV	Mean	%CV	Mean	Mean	%CV	Mean
20	11	0.77	37.4%	703	16.0%	35.0	283	17.6%	14.2
70	5	0.91	24.3%	2640	24.9%	37.7	1045	22.1%	14.9
88	5	0.84	11.3%	3172	24.9%	36.0	1247	31.3%	14.2

%CV, coefficient of variation; AUC, area under the plasma concentration–time curve; $AUC_{0\ last}$, AUC from 0 to last time point; C_{max}, maximum concentration; PK, pharmacokinetic.

Antitumor Activity

- All 27 patients were included in the response evaluation
- Preliminary findings showed that in the overall population, the ORR was 81%, and the clinical benefit rate (CBR) was 93% **(Table 5)**
  - At the MTD of 70 mg/m^2 (n=15), the ORR was 93% (14/15) and the CBR was 100% (15/15)
- Median time to response for patients who achieved a partial response or better (n=22) was 1.6 months (range, 0.7–7.2)
- Event-free progression-free survival (PFS) rates at 6, 9, and 12 months in the overall population were 79%, 75%, and 75%, respectively

Table 5. Response Results in Response-Evaluable Patients (N=27), Based on Investigator Assessment

	Dose-escalation cohorts				Dose-expansion cohort	
	45 mg/m^2 (n=3)	56 mg/m^2 (n=3)	70 mg/m^2 (n=6)	88 mg/m^2 (n=6)	70 mg/m^2 (n=9)	Overall (N=27)
Best response, n (%)						
Complete response	0	3 (100)	3 (50)	2 (33)	1 (11)	9 (33)
Very good partial response	0	0	1 (17)	0	2 (22)	3 (11)
Partial response	1 (33)	0	1 (17)	2 (33)	6 (67)	10 (37)
Minimal response	1 (33)	0	1 (17)	1 (17)	0	3 (11)
Stable disease	1 (33)	0	0	0	0	1 (4)
Not evaluable	0	0	0	1 (17)	0	1 (4)
ORR, n (%) [95% CI]	1 (33)	3 (100)	5 (83)	4 (67)	9 (100)	22 (81) [61.9–93.7]
Median time to response, months	1.6	1.6	1.6	0.7	1.0	1.6
CBR, n (%) [95% CI]	2 (67)	3 (100)	6 (100)	5 (83)	15 (100)	25 (93) [75.7–99.1]

CBR, clinical benefit rate; CI, confidence interval; ORR, overall response rate.

CONCLUSIONS

- For patients with relapsed or refractory MM, the MTD of once-weekly carfilzomib administered in combination with weekly dexamethasone (40 mg) was 70 mg/m^2
  - In this population, the majority of patients (85%) had received prior treatment with bortezomib; 63% of patients were refractory to bortezomib
- At the MTD, weekly carfilzomib and dexamethasone had an acceptable safety and tolerability profile, with infrequent grade ≥3 AEs, a low rate of discontinuation due to AEs, and no carfilzomib dose reductions
- Weekly carfilzomib (70 mg/m^2) infused over 30 minutes had a mean terminal half-life similar to the currently approved twice-weekly carfilzomib dosing regimen (20/27 mg/m^2 infused over 2–10 minutes), but achieved a lower C_{max}[1,7,8]
- The phase 1 portion of the study has finished enrollment and has shown that weekly carfilzomib in combination with weekly dexamethasone demonstrated promising efficacy (ORR of 81%; CBR of 93%) with a rapid median time to response
- The phase 2 portion of the study is currently enrolling patients (planned enrollment, 127 patients) to further evaluate the efficacy and safety profile of weekly carfilzomib (70 mg/m^2) in combination with dexamethasone (40 mg once weekly) for patients with relapsed or refractory MM

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