Phase I/Ib study of carfilzomib and panobinostat with or without dexamethasone in patients with relapsed/refractory multiple myeloma

Approval of bortezomib revolutionized the treatment of multiple myeloma (MM). Since then, second-generation proteasome inhibitors (PI) (carfilzomib and oral ixazomib) have been developed and approved.[1,2] Panobinostat, a pan-deacetylase inhibitor (HDACi) has been approved in combination with bortezomib and dexamethasone to treat relapsed MM patients who have received ≥ 2 prior lines of therapy including bortezomib and an immunomodulatory drug (IMiD).[3] Two early phase clinical trials evaluating combination of carfilzomib and panobinostat without dexamethasone have shown similar overall response rates (ORR) of more than 60% and progression-free survival (PFS) of eight months, despite using different panobinostat schedules.[4,5]

We conducted an open label, single-center, single-arm trial of panobinostat and carfilzomib in patients with relapsed/refractory MM (RRMM). The primary objective of this Phase I study was to determine the maximum recommended dose from the four pre-planned dose levels (Table 1). The primary objective in Phase Ib was to determine the overall response rate of the combination per International Myeloma Working Group (IMWG) Uniform Response Criteria for MM.[6] Secondary end points were PFS and overall survival (OS). To be eligible, patients needed to have RRMM and ≥ 2 lines of prior therapy including at least one IMiD and PI. Detailed eligibility criteria are provided in the *Online Supplementary Appendix*. The protocol was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice. The trial was registered at *clinicaltrials.gov: identifier NCT01301807*.

The Phase Ia used a 3+3 design to evaluate four doses to determine the combination's maximum recommended dose without dexamethasone (Table 1). After eight cycles of therapy, patients could continue with carfilzomib dosing on days 1, 2, 15, 16 and panobinostat as tolerated. Dexamethasone 40 mg weekly could be added at the investigator's discretion during Phase Ib, and 4 mg weekly could be used in patients intolerant to steroids.

Responses were evaluated at each cycle in patients that completed at least one cycle of therapy. Patients who received at least one dose of study drugs were evaluable for toxicity, graded in severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE ver. 4). Time-to-event outcomes, including PFS/OS, were estimated using the Kaplan-Meier method.

A total of 47 patients were enrolled and treated at MD Anderson between August 2nd 2011 and April 29th 2016 (Figure 1). The median age of enrolled patients was 63 years (range 41-76). Patients received a median of four prior lines of therapy (range 2-16) including prior bortezomib (96%), carfilzomib (28%), IMiD (100%), and autologous stem cell transplantation (87%). All patients (100%) were refractory to either bortezomib or IMiD. Ten (10) patients (21%) were high risk by fluorescence *in situ* hybridization (FISH) (*Online Supplementary Table S1*).

Twenty-four patients were treated on Phase Ia and dose-limiting toxicities (DLT) were evaluated after the first cycle of therapy. None of the patients at dose levels 1 and 2 (3 patients each) encountered DLT. One of three patients at dose level 3 encountered DLT (grade 4 thrombocytopenia with bleeding); three additional patients were treated at dose level 3 and, per protocol, dose level 1 was backfilled with three patients. None of these additional patients treated at dose levels 1 and 3 experienced DLT. Three patients were then treated at dose level 4, and dose level 2 was backfilled with three patients; none of the patients at dose level 4 or level 2 experienced DLT. Three patients were added to dose level 4, and of these only one patient experienced a DLT (grade 4 thrombocytopenia with bleeding, grade 4 creatinine increase, grade 3 myalgia). Per protocol, the maximum tolerated dose (MTD) of panobinostat and carfilzomib was not reached. The maximum recommended dose was determined to be dose level 4 (Table 1).

Twenty-three patients were treated at the maximum recommended dose on the Phase Ib expansion for a total of 29 patients (panobinostat 20mg, carfilzomib

Table 1. Dose escalation.

Cohort	Carfilzomib on days 1, 2, 8, 9, 15, 16 every 28 days	Panobinostat on days 1, 3, 5, 8, 10, 12 every 28 days	Patients	Patients with DLT	Maximum recommended dose
1	20 mg/m² cycle 1 days 1 and 2 27 mg/m² for all subsequent doses (20/27 mg/m²)	15 mg	6	0	
2	20 mg/m² cycle 1 days 1 and 2 27 mg/m² for all subsequent doses (20/27 mg/m²)	20 mg	6	0	
3	20 mg/m² cycle 1 days 1 and 2 36 mg/m² for all subsequent doses (20/36 mg/m²)	20 mg	6	1	
4	20 mg/m² cycle 1 days 1 and 2 45 mg/m² for all subsequent doses (20/45 mg/m²)	20 mg	6*	1	X

*One patient withdrew consent after day 8 of cycle 1; DLT: dose-limiting toxicity.

20/45mg/m^2) (Table 1); 15 (52%) and two (7%) of those patients also received 40 mg and 4 mg dexamethasone weekly, respectively. Patients completed a median of three cycles of therapy (range 1-25). Reasons for discontinuation are shown in Figure 1.

Forty-six of 47 dosed patients were evaluable for response (Table 2). The ORR (≥ PR) in all 46 evaluable patients was 37% and clinical benefit rate (CBR; ≥ MR) was 54%. ORR was lower in patients refractory to PI (30%), IMiD (32%), and both (17%). Presence of high risk defined by FISH (*Online Supplementary Table S1*) also decreased the ORR rate (25%).

The ORR at the maximum recommended dose (n=28) was 39% and CBR was 54% (Table 2). Notable differences were seen between patients treated with (n=17) or without (n=11) dexamethasone; ORR of 53% *versus* 18% and CBR of 65% *versus* 36%, respectively. In patients treated with dexamethasone, ORR and CBR were lower in those refractory to IMiD (43% and 57%) and in dual refractory patients (33% and 50%) (*Online Supplementary Table S2*).

At a median follow up of 66 months (32-83 months), the PFS and OS for all patients (n=47) was 3.35 months and 15.1 months, and for patients treated at the maximum recommended dose (n=29) these were 3.02 months and 17.2 months, respectively (*Online Supplementary Figure S1*). OS was longer for patients treated at the maximum recommended dose with dexamethasone *versus* no dexamethasone (18.2 *vs.* 10.1 months) (*Online Supplementary Figure S2*).

A summary of all treatment-related toxicities is provided in *Online Supplementary Tables S3 and S4*. Grade 3 and 4 hematologic adverse events (AE) were thrombocytopenia (29 of 47, 62%), anemia (25 of 47, 53%), neutropenia (19 of 47, 40%), and decreased white blood cell (WBC) count (6 of 47, 13%). The most frequent non-hematologic Grade 3/4 AE were fatigue (8 of 47, 17%), elevated creatinine (6 of 47, 13%), and lung infection (including pneumonia; 6 of 47, 13%). All other grade 3/4 AE were reported in less than 10% of patients. Drug dosing had to be interrupted/delayed or reduced in 52% (24 of 46) of all patients and in 48% (14 of 29) of patients treated at the maximum recommended dose (*Online Supplementary Figure S3*).

The ORR of 39% achieved in our study is similar to the phase II PANORAMA-2 clinical trial (ORR 35%) that tested bortezomib/panobinostat/dexamethasone in relapsed and bortezomib-refractory MM. However, the rate of IMiD-refractory patients was not reported in that study.[7] It is also in line with a 41% ORR reported in a phase II study of panobinostat/lenalidomide, in which 52% of patients were bortezomib-refractory and 81% lenalidomide-refractory.[8] Our 39% ORR is higher than the 24% reported with single-agent carfilzomib, where 73% of patients were refractory to bortezomib,[9] but it is lower than the 61% achieved in the phase III PANORAMA-1 study, in which patients had received only 1-3 lines of prior therapy and none were refractory to bortezomib.[3] The PANORAMA-1 study showed positive effect of panobinostat on ORR and PFS in patients that had received at least two prior lines of therapy including bortezomib and IMiD, and led to the US Food and Drug Administration approval of panobinostat/bortezomib/dexamethasone for RRMM.

The ORR of 39% in our study is also lower than the 63% reported in two early phase studies of

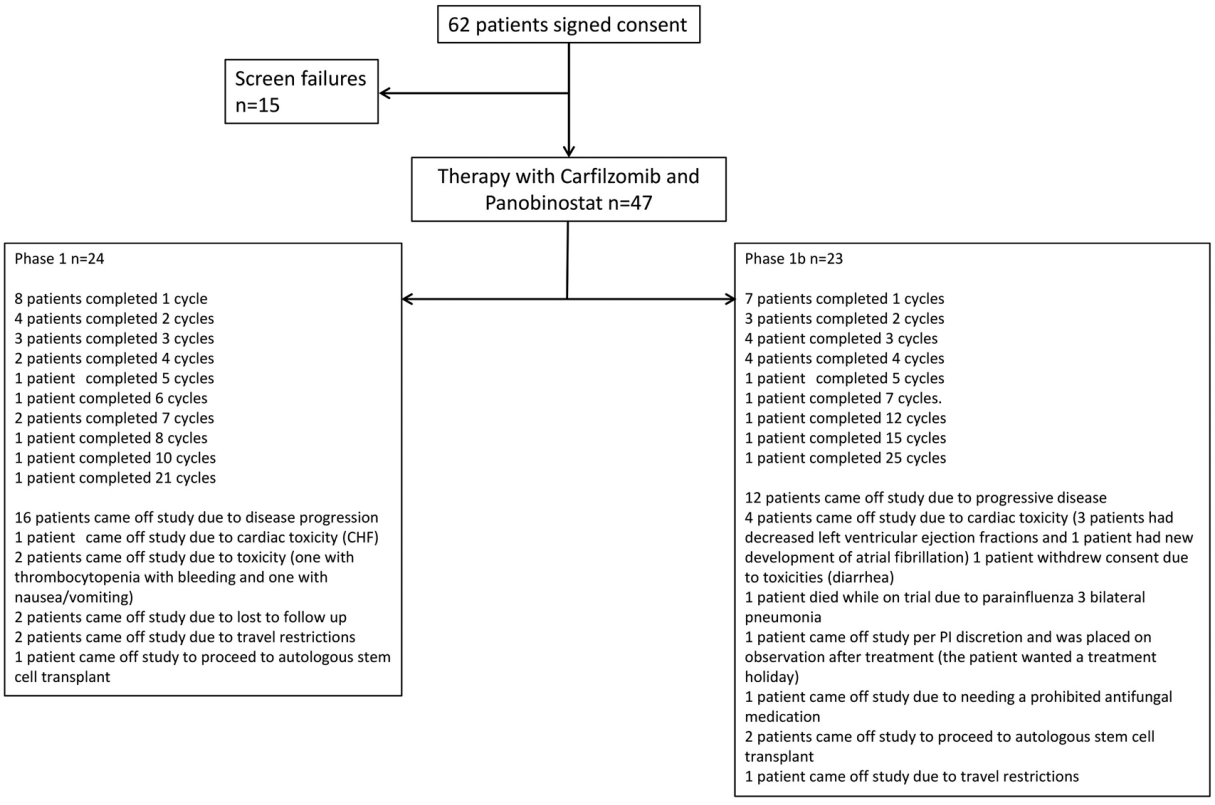

Figure 1. Trial flow chart. CHF: congestive heart failure.

Table 2. Best response to treatment in all evaluable patients.

Response assessment	All evaluable patients n=46	Phase Ia n=23	Phase Ib n=23	MRD n=28	MRD with dex n=17	MRD w/o dex n=11	MRD Prior PI# n=27	MRD ref. to btz n=21	MRD ref. to cfz n=11	MRD ref. to IMiD n=25	MRD dual* ref. n=22
ORR, n	17	7	10	11	9	2	11	8	3	8	5
(%)	*37.0*	*30.4*	*43.5*	*39.3*	*52.9*	*18.2*	*40.7*	*38.1*	*27.3*	*32.0*	*22.7*
CBR, n	25	12	13	15	11	4	15	11	4	12	9
(%)	*54.3*	*52.2*	*56.5*	*53.6*	*64.7*	*36.4*	*55.6*	*52.4*	*36.4*	*48.0*	*40.9*
CR, n	1	0	1	1	1	0	1	1	1	0	0
(%)	*2.2*	*0.0*	*4.3*	*3.6*	*5.9*	*0.0*	*3.7*	*4.8*	*9.1*	*0.0*	*0.0*
VGPR, n	5	2	3	3	2	1	3	1	1	3	1
(%)	*10.9*	*8.7*	*13.0*	*10.7*	*11.8*	*9.1*	*11.1*	*4.8*	*9.1*	*12.0*	*4.5*
PR, n	11	5	6	7	6	1	7	6	1	5	4
(%)	*23.9*	*21.7*	*26.1*	*25.0*	*35.3*	*9.1*	*25.9*	*28.6*	*9.1*	*20.0*	*18.2*
MR, n	8	5	3	4	2	2	4	3	1	4	4
(%)	*17.4*	*21.7*	*13.0*	*14.3*	*11.8*	*18.2*	*14.8*	*14.3*	*9.1*	*16.0*	*18.2*
SD, n	7	3	4	4	2	2	3	2	3	4	4
(%)	*15.2*	*13.0*	*17.4*	*14.3*	*11.8*	*18.2*	*11.1*	*9.5*	*27.3*	*16.0*	*18.2*
PD n	14	8	6	9	4	5	9	8	4	9	9
(%)	*30.4*	*34.8*	*26.1*	*32.1*	*23.5*	*45.5*	*33.3*	*38.1*	*36.4*	*36.0*	*40.9*

CR: complete response; VGPR: very good partial response; PR: partial response: ORR: overall response rates (CR+VGPR+PR); CBR: clinical benefit rate (CR+VGPR+PR+MR); MRD: maximum recommended dose; dex: dexamethasone; btz: bortezomib; cfz: carfilzomib; n: number; w/o: without; PI: proteasome inhibitor; ImiD: immunomodulatory drug. #Prior exposure to either btz or cfz.

carfilzomib/panobinostat without dexamethasone.[4,5] However, when compared to our study, those patients were significantly less refractory to bortezomib (68% *vs.* 36% and 53%), carfilzomib (28% *vs.* 0% in both), lenalidomide (87% *vs.* 14% and 31%), or both PI and IMiD (66% *vs.* 25% and not reported).

Dose-limiting toxicities observed during dose escalation included two grade 4 thrombocytopenias with bleeding, one grade 3 myalgia, and one grade 4 creatinine increase. The most common hematologic AE was grade 3/4 thrombocytopenia in 64% of patients, which is higher than the 38% and 41% reported previously.[4,5] In comparison, our patients had similar rates of grade 3/4 fatigue (17% *vs.* 11% and 18%), lower rates of grade 3/4 diarrhea (3% *vs.* 11% and 6%) and grade 3/4 nausea/vomiting (7% *vs.* 21% and 12%), a similar rate of discontinuation for toxicity (17% *vs.* 11% and 19%) but less dose reductions (21% *vs.* 59% and 43%) than reported by Berdeja and Kaufman, respectively.[4,5] Cardiac toxicities in our study were limited to grade 1/2 (17%) and 3 (13%). Only one patient (2%) had a grade 1 QTc prolongation while on study.

In conclusion, two prior studies have shown that carfilzomib can be safely combined with panobinostat to produce high response rates (63%) in patients with RRMM. Our study confirms these results in patients with a higher degree of PI and IMiD refractoriness and, for the first time, carfilzomib refractory patients, albeit with a lower ORR (39%), PFS (3 months), and OS (17.2 months). This regimen could be used as a bridge therapy in patients that are highly refractory or if other therapies are not readily available. This is also the first study to report the efficacy and safety of carfilzomib/panobinostat with weekly dexamethasone, the addition of which improved ORR from 18% to 53% and prolonged OS from 10 to 18.2 months. Despite the limitations of the study (small number of patients in each group with or without dexamethasone and lack of power/randomization), the findings of improved response with dexamethasone are interesting and warrant larger randomized studies to provide a definite answer.

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