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RESEARCH ARTICLE

Weekly carfilzomib, lenalidomide, and dexamethasone in relapsed or refractory multiple myeloma: A phase 1b study

Noa Biran[1] | David Siegel[1] | Jesus G. Berdeja[2] | Noopur Raje[3] | Robert Frank Cornell[4] | Melissa Alsina[5] | Tibor Kovacsovics[6] | Belle Fang[7] | Amy S. Kimball[8] | Ola Landgren[9]

[1]Myeloma Division, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, New Jersey

[2]Department of Medicine, Sarah Cannon Research Institute, Nashville, Tennessee

[3]Department of Hematology and Oncology, Massachusetts General Hospital Cancer Center, Boston, Massachusetts

[4]Division of Hematology and Oncology, Vanderbilt University Medical Center, Nashville, Tennessee

[5]Department of Blood and Marrow Transplantation, Moffit Cancer Center, Tampa, Florida

[6]Division of Hematology and Hematologic Malignancies, Department of Internal Medicine, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, Utah

[7]Global Biostatistical Science, Amgen Inc., Thousand Oaks, California

[8]Global Development, Amgen Inc., Thousand Oaks, California

[9]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City, New York

Correspondence
Noa Biran, MD, Myeloma Division, John Theurer Cancer Center, Hackensack University Medical Center, 92 Second Street, Suite 340, Hackensack, NJ 07631.
Email: noa.biran@hackensackmeridian.org

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Abstract

Twice-weekly carfilzomib (27 mg/m^2) with lenalidomide-dexamethasone (KRd) is a standard-of-care in relapsed or refractory multiple myeloma (RRMM). This phase 1b study evaluated KRd with once-weekly carfilzomib in RRMM. Patients received carfilzomib (30-minute infusion; 56 or 70 mg/m^2) on days 1, 8, and 15; lenalidomide 25 mg on days 1-21; and dexamethasone 40 mg on days 1, 8, 15, and 22 (day 22 omitted for cycles 9+) of 28-day cycles. Primary objective was safety/tolerability; efficacy was a secondary objective. Fifty-six RRMM patients enrolled: 22 during dose evaluation (56-mg/m^2, n = 10; 70-mg/m^2, n = 12) and 34 during dose expansion (all initiated dosing at 70 mg/m^2). After 2 fatal adverse events (AEs) during 70-mg/m^2 dose expansion, dosage reduction to 56 mg/m^2 was permitted. Results are presented for carfilzomib 56-mg/m^2 (n = 10) and 70-mg/m^2 groups (dose evaluation/expansion; n = 46). Median carfilzomib dose was 53.2 mg/m^2 (56-mg/m^2 group) and 62.4 mg/m^2 (70-mg/m^2 group). Grade ≥3 AE rates were 70.0% (56 mg/m^2) and 69.6% (70 mg/m^2). Overall response rates were 90.0% (56 mg/m^2) and 89.1% (70 mg/m^2); ≥very good partial response rates were 50.0% (56 mg/m^2) and 73.9% (70 mg/m^2). Once-weekly KRd was active with acceptable toxicity in RRMM, supporting further evaluation of this regimen.

1 | INTRODUCTION

Despite advances in the treatment and management of multiple myeloma (MM) over the past 15 years, relapsed and/or refractory MM remains a common and life-threatening diagnosis.[1,2] Optimal therapy given at first relapse of MM is important for achieving maximal treatment response and prolonged survival.[3-5] Compared with subsequent relapses, the disease at first relapse is more sensitive to treatment, as there are fewer genetic alterations conferring drug resistance.[6] Consistent with this, overall response rates (ORRs) and duration of response have been found to progressively decline with each successive relapse.[6,7] In addition, a substantial portion of patients with relapsed MM may not receive treatment beyond second-line therapy due to death or other reasons, suggesting that for some patients with relapsed disease, the first relapse may be the only opportunity to receive optimal therapy.[8] Overall, these considerations underscore the importance of early administration of effective therapies to achieve deep responses at first relapse.

Carfilzomib is an irreversible and specific second-generation proteasome inhibitor used for the treatment of relapsed or refractory MM (RRMM). In the randomized, phase 3 ASPIRE study, triplet therapy with carfilzomib (given twice weekly on two consecutive days as an intravenous [IV] infusion), lenalidomide, and dexamethasone (KRd) vs treatment with lenalidomide and dexamethasone (Rd) alone resulted in ORRs of 87.1% vs 66.7%, very good partial response (VGPR) or better rates of 69.9% vs 40.4%, median progression-free survival (PFS) durations of 26.3 vs 17.6 months (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.57-0.83; P = .0001), and median overall survival (OS) durations of 48.3 vs 40.4 months (HR, 0.79; 95% CI, 0.67-0.95; P = .0045) in patients with RRMM.[9,10]

To improve convenience and lessen the burden on patients and the healthcare system, a less-frequent once-weekly carfilzomib dosing schedule has been investigated. In previous studies, once-weekly carfilzomib with dexamethasone has been found to be an effective and well-tolerated regimen for patients with RRMM.[11,12] Given the established efficacy of twice-weekly KRd in RRMM, and the potential for improved convenience with once-weekly carfilzomib dosing, we initiated a phase 1b study exploring once-weekly KRd in patients with RRMM and newly diagnosed MM (NDMM). The primary objective of the study was assessment of the safety and tolerability of once-weekly KRd; efficacy was a secondary endpoint.

2 | METHODS

2.1 | Study design and participants

This was an open-label, multicenter, phase 1b, dose-finding study of once-weekly KRd (ClinicalTrials.gov Identifier: NCT02335983). The study enrolled patients with RRMM and NDMM. Results for the RRMM patient cohort are presented here. Analysis of the NDMM cohort (~50 patients) is currently ongoing and will be presented separately.

Adult patients with RRMM (one-three prior lines of therapy) were eligible if they had achieved at least a partial response (PR) to one prior line of therapy (ie, patients with primary refractory MM were ineligible). Patients must have had an Eastern Cooperative Oncology Group performance status of 0-2, left-ventricular ejection fraction of ≥40%, and calculated or measured creatinine clearance of ≥50 mL/min within 21 days before cycle one, day one. Patients with RRMM were ineligible if they were previously treated with an Rd-containing combination and progressed within the first three months of treatment initiation. Patients were also excluded if they had any disease progression during treatment if an Rd-containing regimen was the most recent line of therapy; progression on maintenance lenalidomide was allowed. Prior carfilzomib or oprozomib treatment was not permitted. Other exclusion criteria included contraindications to lenalidomide or dexamethasone; active congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, acute diffuse infiltrative pulmonary disease, pericardial disease, or myocardial infarction (MI) within six months before cycle one, day one; and significant neuropathy (grade ≥3) within 14 days before cycle one, day one.

The study had two parts: a dose-evaluation component and a dose-expansion component. The dose-evaluation component consisted of two carfilzomib dosing cohorts: 56 and 70 mg/m^2. Eight patients evaluable for dose-limiting toxicities (DLTs) were planned for enrollment in each cohort. Patients were considered DLT-evaluable if they received all planned doses of carfilzomib, at least 80% of planned doses of lenalidomide, and at least 75% of planned doses of dexamethasone, or received ≥1 dose of carfilzomib and had a DLT prior to completion of study treatment for cycle one. If a DLT was reported in fewer than three patients enrolled in a dose-evaluation cohort, that cohort was considered eligible for dose expansion. A cohort safety review committee consisting of the lead investigator, selected additional investigators, the sponsor medical monitor, and the sponsor's drug safety representative, reviewed all evaluable safety data from the dose-evaluation component before selecting the KRd regimen to be used in the dose-expansion component. A dose of 70 mg/m^2 was selected for dose expansion.

The study protocol was approved by the ethics committees or institutional review boards of all participating institutions. All patients provided written informed consent.

2.2 | Treatment

KRd was administered in 28-day cycles for a maximum of 18 cycles or until disease progression, patient withdrawal, stem cell transplant, or death. Patients received carfilzomib once weekly (30-minute IV infusion) on days 1, 8, and 15. In the dose-evaluation component of the study, patients received carfilzomib 20 mg/m^2 on cycle one, day one, and then 56 or 70 mg/m^2 starting on cycle one, day eight. In the dose-expansion component of the study, patients received KRd on the same schedule. All patients also received oral lenalidomide 25 mg once daily on days 1-21 and dexamethasone 40 mg (oral or IV) on days 1, 8, and 15. Dexamethasone was also given on day 22 for cycles 1-8.

IV hydration (250-500 mL normal saline or appropriate IV fluid) was administered before each carfilzomib infusion during cycle one. Patients received antiviral prophylaxis with valacyclovir and venous thromboembolic

prophylaxis with aspirin (or other anticoagulant or antiplatelet medication). Patients at high risk for tumor lysis syndrome received allopurinol (or other approved uric acid-lowering agent) at the investigator's discretion.

2.3 | Assessments

The primary objective was to assess the safety and tolerability of once-weekly KRd. The clinical activity (efficacy) of once-weekly KRd was assessed as a secondary objective. Safety and efficacy analyses were based upon the safety population, defined as patients who had received at least one dose of study drug, and performed by dosing level of carfilzomib.

Safety and tolerability were evaluated according to the type, incidence, and severity (assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03) of adverse events (AEs). Treatment-emergent AEs (TEAEs) were summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, version 21.0. Select AEs of interest (acute renal failure and cardiac failure) were coded using standardized MedDRA query narrow grouped terms. Monitoring for AEs was performed throughout treatment, and for 30 days after the last administration of study treatment. DLTs were evaluated during cycle one. To qualify as a DLT, an event had to meet the following definitions and be attributable to carfilzomib, lenalidomide, or dexamethasone: non-hematologic DLTs were defined as any grade ≥3 non-hematologic toxicity (excluding nausea/vomiting/diarrhea unless uncontrolled by maximal antiemetic/anti-diarrheal therapy, alopecia, fatigue persisting <14 days, and increased serum creatinine or electrolyte abnormalities deemed not clinically significant and which required no treatment) or grade ≥3 acute kidney injury persisting for >72 hours. Hematologic DLTs were defined as grade 4 neutropenia that persisted for >7 days, febrile neutropenia (any duration), grade 4 thrombocytopenia that persisted for >14 days with or without platelet transfusion and despite holding treatment, or grade ≥3 thrombocytopenia with grade >1 bleeding.

Disease response and progression was assessed by investigators and based on International Myeloma Working Group Uniform Response Criteria.[13,14] ORR was defined as the proportion of patients who achieved a PR or better. PFS was defined as the time from the first day of study treatment to the earlier of disease progression or death due to any cause. Summary statistics for PFS were calculated using the Kaplan-Meier method.

Cytogenetic analyses were performed in a central laboratory. Patients with chromosomal abnormalities t(4;14)[≥10%], t(14;16)[≥10%], and/or deletion17p[≥20%] were included in the high-risk cytogenetics group. Patients with normal cytogenetics or other chromosomal abnormalities were included in the standard-risk group.

2.4 | Data sharing

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

3 | RESULTS

3.1 | Patients and enrollment

Patients were enrolled between April 20, 2015 and August 15, 2016. The data cutoff date for this analysis was July 19, 2018. At the time of data cutoff, no patients remain on treatment, two remain in active follow up, and 54 were off study. A total of 56 patients with RRMM were enrolled: 22 in the dose-evaluation portion of the study (56-mg/m^2 group, n = 10; 70-mg/m^2 group, n = 12), and 34 in the dose-expansion portion (all initiated therapy at 70 mg/m^2) (Figure S1).

Across the dose-evaluation and dose-expansion portions of the study, the median age of patients with RRMM was 68.5 years (range, 55-87) in the 56-mg/m^2 group and 63.5 years (range, 34-81) in the 70-mg/m^2 group (Table 1). Four patients (40.0%) in the 56-mg/m^2 group and 16 patients (34.8%) in the 70-mg/m^2 group were refractory to lenalidomide given in a prior line, and six patients (60%) in the 56-mg/m^2 group and 14 patients (30.4%) in the 70-mg/m^2 group were refractory to prior bortezomib. Six patients (60.0%) in the 56-mg/m^2 group and 33 (71.7%) in the 70-mg/m^2 group received prior stem cell transplant. One patient (10.0%) in the 56-mg/m^2 group and six (13.0%) in the 70-mg/m^2 group had high-risk cytogenetics.

Of the 56 RRMM patients enrolled, seven underwent stem cell mobilization, nine received an autologous stem cell transplant, and one received an allogeneic stem cell transplant after study therapy.

3.2 | Dose evaluation

Among DLT-evaluable patients, there were no DLTs observed in either the 56- or 70-mg/m^2 dose-evaluation cohorts. The 70-mg/m^2 dosing level was selected for dose expansion. Two fatal serious AEs occurred after the 70-mg/m^2 dose expansion cohort was fully enrolled. One patient died of a documented MI after cycle 1, day 8 dosing. A second patient was found at home after cycle 2, day 8 dosing; no autopsy was done, and the investigator attributed the death to cardiac disorder. Based on discussions with the investigators, it was determined that patients in the dose-expansion cohort could continue to be dosed at 70 mg/m^2 or could have their dose reduced to 56 mg/m^2 per investigator discretion.

3.3 | Treatment exposure and safety

Exposure and safety results are presented for all RRMM patients treated during the study (56 mg/m^2, n = 10; 70 mg/m^2, n = 46). The median across patients for carfilzomib dose received for each patient was 53.2 mg/m^2 in the 56-mg/m^2 group and 62.4 mg/m^2 in the 70-mg/m^2 group, and the mean dose was 52.8 mg/m^2 and 61.3 mg/m^2, respectively. The mean relative dose intensity (SD) of carfilzomib was 89.2% (9.46) in the 56-mg/m^2 group and 87.7% (9.96) in the 70-mg/m^2 group. Two of ten patients (20%) in the 56-mg/m^2 group had their carfilzomib dose reduced to 45 mg/m^2 (both dose reductions were due to AEs) (Figure 1). Twenty-two of 46 patients (48%) in the 70-mg/m^2 group had their carfilzomib dose reduced to 56 mg/m^2 or 45 mg/m^2 (eight of the 22 dose reductions were

TABLE 1 Patient demographics and baseline disease characteristics

	Carfilzomib 56 mg/m^2 (N = 10)	Carfilzomib 70 mg/m^2 (N = 46)
Sex, n (%)		
Male	7 (70.0)	26 (56.5)
Median age, years (range)	68.5 (55-87)	63.5 (34-81)
ECOG performance status, n (%)		
0	6 (60.0)	24 (52.2)
1	4 (40.0)	22 (47.8)
ISS stage, n (%)		
I	6 (60.0)	27 (58.7)
II	2 (20.0)	13 (28.3)
III	1 (10.0)	1 (2.2)
Unknown	1 (10.0)	5 (10.9)
Cytogenetic risk group (central lab),[a] n (%)		
High	1 (10.0)	6 (13.0)
Standard	6 (60.0)	21 (45.7)
Unknown	3 (30.0)	19 (41.3)
Number of prior regimens, n (%)		
1	5 (50.0)	27 (58.7)
2	0	9 (19.6)
3	5 (50.0)	9 (19.6)
4	0	1 (2.2)
Refractory to,[b] n (%)		
Bortezomib	6 (60.0)	14 (30.4)
Ixazomib	0	0
Lenalidomide	4 (40.0)	16 (34.8)
Thalidomide	0	0
Pomalidomide	2 (20.0)	3 (6.5)
Prior transplant, n (%)	6 (60.0)	33 (71.7)

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

[a]Patients with chromosomal abnormalities t(4;14)[10% or higher], t(14;16)[10% or higher], and/or deletion17p[20% or higher] were included in the high-risk group. Patients with normal cytogenetics or other chromosomal abnormalities were included in the standard-risk group.

[b]Patients were classified as refractory to prior treatment if the best response to prior treatment was stable or progressive disease, disease progression was the specific reason for treatment discontinuation, or if disease progression occurred within 60 days of treatment discontinuation.

due to AEs; four dose reductions were due to investigator discretion; and ten dose reductions did not have a reason given) (Figure 1).

Among patients treated in either portion of the study, the median number of KRd cycles that patients received was 10.0 (range, 3-18) in the 56-mg/m^2 group and 7.5 (range, 1-18) in the 70-mg/m^2 group. A total of 14 patients (56-mg/m^2 group, n = 1 [10.0%]; 70-mg/m^2 group, n = 13 [28.3%]) completed 18 cycles of therapy.

At least one TEAE occurred in all patients. The patient incidence of the most common TEAEs is shown in Table 2. The most common non-hematologic AEs were fatigue, diarrhea, upper respiratory tract infection, and nausea. The most common hematologic AEs were thrombocytopenia and anemia. The patient incidence of grade ≥3 TEAEs in the 56- and 70-mg/m^2 groups was 70.0% and 69.6%, respectively. Common grade ≥3 non-hematologic AEs (>2 patients) were pneumonia, hypertension, and hypophosphatemia. Common grade ≥3 hematologic AEs (>2 patients) were thrombocytopenia, neutropenia, and anemia. Grade ≥3 cardiac failure (grouped term) occurred in one patient in the 70-mg/m^2 group, and grade ≥3 acute renal failure (grouped term) occurred in one patient in each of the 56- and 70-mg/m^2 groups.

The incidence of treatment-emergent serious AEs was 40.0% in the 56-mg/m^2 group and 34.8% in the 70-mg/m^2 group. No deaths due to AEs were reported in the 56-mg/m^2 group. Two deaths due to AEs were reported in the 70-mg/m^2 group, which were due to cardiac arrest in a patient who received one cycle of treatment and cardiac disorder in a patient who received two cycles of treatment (as described above).

3.4 | Efficacy

The ORRs were 90.0% in the 56-mg/m^2 group and 89.1% in the 70-mg/m^2 group. A VGPR or better was observed in 50.0% and 73.9% of patients in the two groups, respectively. A complete response (CR) or better in 20.0% and 30.4% of patients in the two groups, and a stringent CR in 10.0% and 17.4% of patients in the 2 groups was reported (Table 3). Among all patients (n = 56), the ORR was 89.3%, the ≥VGPR rate was 69.6%, and the ≥CR rate was 28.6%.

Median PFS was not reached in either the 56-mg/m^2 group (95% CI, 14.8 months-not evaluable [NE]) or the 70-mg/m^2 group (95% CI, 21.1 months-NE). As of the data cutoff date, 1 patient (10.0%) in the 56-mg/m^2 group and 7 patients (15.2%) in the 70-mg/m^2 group experienced disease progression.

4 | DISCUSSION

A twice-weekly KRd regimen using a carfilzomib dose of 27 mg/m^2 has been shown to have a favorable benefit-risk profile and is a standard-of-care regimen for patients with RRMM.[9,10,15] This study investigated a more convenient KRd regimen using once-weekly carfilzomib (56 and 70 mg/m^2) for patients with RRMM. In the dose-evaluation portion of the study, no DLTs were reported and once-weekly KRd with carfilzomib 70 mg/m^2 was selected for dose expansion.

After two deaths were observed during cycle one or two Among 46 patients with RRMM who began therapy at 70 mg/m^2, investigators were allowed to reduce the dose to 56 mg/m^2 at their discretion. A third RRMM patient died on study, due to progressive disease. No other deaths have occurred on study. Other early phase RRMM studies have reported deaths in early cycles. For example, Berenson and colleagues evaluated accelerated elotuzumab infusion in 70 patients with NDMM or RRMM, and reported two deaths (due to ischemic colitis and chronic obstructive lung disease) that occurred in patients who received only one cycle of treatment.[16] Seven deaths were reported among 46 patients enrolled into a phase 1b study of panobinostat, lenalidomide, and

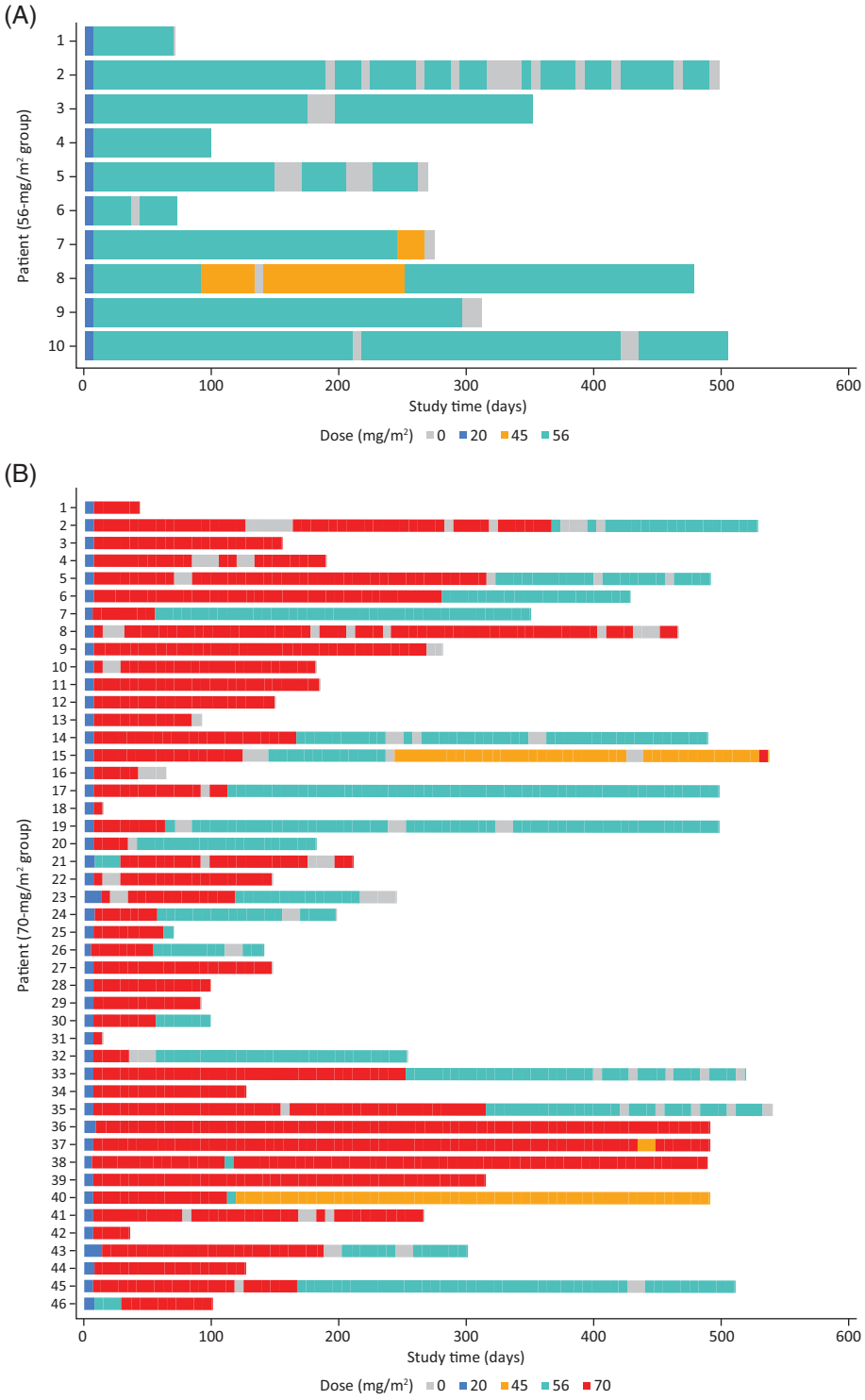

FIGURE 1 Swimmers plots for exposure to carfilzomib in the (A) 56-mg/m^2 group and (B) 70-mg/m^2 group

dexamethasone.[17,18] In a phase one study of pomalidomide, bortezomib, and dexamethasone in lenalidomide-refractory and proteasome inhibitor-exposed relapsed or relapsed and refractory MM patients (n = 34), one patient died in cycle three due to cardiac arrest.[19]

In this study, once-weekly KRd had acceptable toxicity. The incidence of grade ≥3 AEs observed with once-weekly KRd (56 mg/m^2, 70.0%; 70 mg/m^2, 69.6%) were lower than previously reported for the twice-weekly KRd regimen in the ASPIRE study (83.7%).[10] Overall, the safety profile observed with once-weekly KRd was consistent with the safety profile for twice-weekly KRd in the ASPIRE study.[10] There were no patients who experienced cardiac arrest, cardiac disorder, or cardiac failure in the 56-mg/m^2 group; in the 70-mg/m^2 group, one patient had grade ≥3 cardiac failure, and two other patients had fatal cardiac events (cardiac arrest and cardiac disorder).

Once-weekly KRd demonstrated promising efficacy in this study, with similar ORRs for both dosing levels (56 mg/m^2, 90.0%; 70 mg/m^2, 89.1%)

TABLE 2 Treatment-emergent adverse events

	Carfilzomib 56 mg/m^2 (N = 10)		Carfilzomib 70 mg/m^2 (N = 46)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any-grade AEs in ≥25% of patients in a cohort or grade ≥3 AEs in >1 patient in a cohort, n (%)				
Fatigue	5 (50.0)	0	25 (54.3)	1 (2.2)
Diarrhea	5 (50.0)	0	23 (50.0)	2 (4.3)
Upper respiratory tract infection	3 (30.0)	0	20 (43.5)	1 (2.2)
Thrombocytopenia	6 (60.0)	3 (30.0)	21 (45.7)	6 (13.0)
Nausea	5 (50.0)	0	15 (32.6)	0
Cough	3 (30.0)	0	16 (34.8)	1 (2.2)
Dyspnea	4 (40.0)	0	13 (28.3)	1 (2.2)
Muscle spasms	2 (20.0)	0	16 (34.8)	0
Constipation	3 (30.0)	0	14 (30.4)	0
Dizziness	5 (50.0)	0	10 (21.7)	0
Insomnia	4 (40.0)	1 (10.0)	9 (19.6)	1 (2.2)
Muscular weakness	1 (10.0)	0	12 (26.1)	1 (2.2)
Anemia	3 (30.0)	2 (20.0)	10 (21.7)	4 (8.7)
Pyrexia	5 (50.0)	0	8 (17.4)	0
Asthenia	3 (30.0)	0	3 (6.5)	1 (2.2)
Deep vein thrombosis	3 (30.0)	0	2 (4.3)	0
Myalgia	3 (30.0)	0	2 (4.3)	0
Leukopenia	3 (30.0)	1 (10.0)	1 (2.2)	0
Neutropenia	4 (40.0)	3 (30.0)	11 (23.9)	7 (15.2)
Hypertension	1 (10.0)	1 (10.0)	11 (23.9)	3 (6.5)
Hypophosphatemia	0	0	4 (8.7)	4 (8.7)
Pneumonia	1 (10.0)	0	4 (8.7)	4 (8.7)

Note: Adverse events (AEs) reported as preferred term. Neutropenia included both neutropenia and neutrophil count decreased preferred terms; thrombocytopenia included both thrombocytopenia and platelet count decreased preferred terms.

TABLE 3 Response as determined by investigators

	Carfilzomib 56 mg/m^2 (N = 10)	Carfilzomib 70 mg/m^2 (N = 46)
Best overall response, n (%)		
Stringent complete response	1 (10.0)	8 (17.4)
Complete response	1 (10.0)	6 (13.0)
Very good partial response	3 (30.0)	20 (43.5)
Partial response	4 (40.0)	7 (15.2)
Stable disease	1 (10.0)	4 (8.7)
Not evaluable	0	1 (2.2)
Overall response rate, n (%)	9 (90.0)	41 (89.1)
Median time to response,[a] days (range)	30.0 (29-91)	29.0 (14-141)

[a]Time from the first dose date of any study drug to the earliest date of a confirmed response of partial response or better.

in an intention-to-treat analysis. These ORRs are comparable to the ORR of 87.1% previously reported for twice-weekly KRd in the ASPIRE study.[10] The rate of CR or better among all patients enrolled in the study was 28.6% (30.4% in the 70-mg/m^2 group; 20.0% in the 56-mg/m^2 group), which is similar to that previously reported with twice-weekly KRd in ASPIRE (31.8%).[10] Similarly, the rate of VGPR or better among all patients enrolled in this study was 69.6%, compared with 69.9% in ASPIRE. Median PFS was not reached in either group; the lower bounds of the 95% CI for median PFS were 14.8 months (56 mg/m^2) and 21.1 months (70 mg/m^2), as compared with 23.3 months reported for twice-weekly KRd in ASPIRE (it should be noted that length of treatment exposure differed between studies).[10] In a previous study of once-weekly KRd (with carfilzomib 56 mg/m^2) conducted in patients with early relapsed and refractory MM (n = 28; median of 1 prior line of therapy), the ≥VGPR rate was 75% and the ≥CR rate was 36%.[20] The 26-month projected PFS and OS rates were 63% and 85%, respectively.[20]

Taken altogether, the results reported here further support the promising efficacy of a once-weekly KRd regimen for patients with RRMM. In the dose-evaluation portion of the present study, the maximum tolerated dose was not determined and similar ORRs were observed between the two dose groups, demonstrating similar efficacy between the 56-mg/m^2 dose and the 70-mg/m^2 dose. Median PFS was not yet reached in either dose group. However, two deaths due to AEs were observed at the 70-mg/m^2 dose level in the expansion cohort, and about half of the

patients in the 70-mg/m^2 group had a dose reduction. The median carfilzomib dose received among patients in the 70-mg/m^2 dose group was 62.4 mg/m^2. The 56-mg/m^2 dose has been selected for further clinical evaluation in a randomized phase three study.

In the present study, the proportion of patients achieving a response with a once-weekly KRd regimen was similar to that observed with twice-weekly KRd in ASPIRE, suggesting comparable efficacy for once-weekly KRd vs twice-weekly KRd. The twice-weekly KRd regimen in the ASPIRE trial has demonstrated OS benefit for patients with RRMM,[9] and the once-weekly KRd regimen evaluated here is similar to the regimen used in ASPIRE. Comparisons between different trials should be interpreted with caution. In the phase 3 TOURMALINE-MM1 trial, the addition of ixazomib to Rd (IRd) was associated with an increase in median PFS from 14.7 to 20.6 months (HR, 0.74; 95% CI, 0.59-0.94; P = .01), an increase in ORR from 72% to 78%, and an increase in the CR rate from 7% to 12% compared with Rd alone.[21] The phase three POLLUX study demonstrated that the addition of daratumumab to Rd (DRd) improved PFS (median, NE vs 18.4 months [HR, 0.37; 95% CI, 0.27-0.52; P < .001]), ORR (92.9% vs 76.4%), and the ≥CR rate (43.1% vs 19.2%) compared with Rd alone.[22] Similarly, in the phase three CASTOR study, the addition of daratumumab to bortezomib and dexamethasone (DVd) improved PFS (median, not estimable vs 7.2 months [HR, 0.39; 95% CI, 0.28-0.53; P < .001]), ORR (82.9% vs 63.2%), and the ≥CR rate compared with Vd alone (19.2% vs 9.0%).[23] The ORRs observed here for the triplet regimen of KRd with once-weekly carfilzomib (56 mg/m^2, 90.0%; 70 mg/m^2, 89.1%) are similar to or higher than ORRs reported for other triplet therapies recommended by the National Comprehensive Care Network guidelines, including IRd, DRd, and DVd.

The twice-weekly dosing schedule for carfilzomib was based on early pre-clinical data, showing that a consecutive day schedule was more effective than once-weekly or non-consecutive day, twice-weekly schedules that allowed recovery of proteasome activity between doses.[24,25] Based on these data, the consecutive day twice-weekly schedule was used in early clinical trials, most often with carfilzomib infused over two to ten minutes.[25] Since this early pre-clinical data, new insight has emerged regarding the effect of infusion time on the pharmacokinetics and pharmacodynamics of carfilzomib, as well as on the dosage that can be given safely and effectively. This, in turn, has expanded the dosing schedules for this agent. One pre-clinical study demonstrated that a 30-minute infusion of carfilzomib resulted in less toxicity and similar levels of proteasome inhibition as an IV bolus,[26] suggesting that a 30-minute infusion would allow higher doses of carfilzomib than the originally approved 27-mg/m^2 dose (given as a 2- to 10-minute infusion) to be administered. The ENDEAVOR study demonstrated that a higher dose (56 mg/m^2) of carfilzomib administered as a twice-weekly, 30-minute infusion was safe and effective in patients with RRMM.[27,28] Using a high dose of carfilzomib (70 mg/m^2) with a 30-minute infusion time, the phase 1/2 CHAMPION-1 study demonstrated that a once-weekly carfilzomib dosing schedule was feasible and effective in patients with relapsed or relapsed and refractory MM.[11] Based on the design of CHAMPION-1, the phase 3 A.R.R.O.W. study showed that treatment with once-weekly carfilzomib (70 mg/m^2) significantly improved PFS compared with twice-weekly carfilzomib (27 mg/m^2). These data supported the recent approval of once-weekly carfilzomib (70 mg/m^2) with dexamethasone for the treatment of patients with RRMM.[12] Other phase 1 and phase 1/2 studies have explored once-weekly carfilzomib across the MM disease continuum, and have thus far demonstrated promising efficacy and tolerability for this schedule.[20,29-32] These studies have explored once-weekly carfilzomib in combination with cyclophosphamide-dexamethasone, pomalidomide-dexamethasone, lenalidomide-dexamethasone, daratumumab-dexamethasone, and daratumumab-lenalidomide-dexamethasone at carfilzomib doses ranging from 27 to 70 mg/m^2. Our study further supports the feasibility of once-weekly carfilzomib in combination with lenalidomide and dexamethasone as a convenient, safe, and effective treatment option for patients with RRMM.

In conclusion, the results from this study demonstrate that carfilzomib administered conveniently on a once-weekly schedule in combination with Rd was active and had manageable toxicity, and the benefit/risk supports additional evaluation of this regimen in patients with RRMM. The 56-mg/m^2 dose will be evaluated further in a randomized phase 3 study.

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CONFLICT OF INTEREST

Noa Biran: Honoraria and speakers' bureau participation for Celgene, Amgen, Takeda, and Sanofi; consulting or advisory role fees and reimbursement of travel, accommodations, or other expenses from Celgene, Amgen, and Takeda; and research funding from Celgene and Amgen.

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AUTHOR CONTRIBUTIONS

DS, MA, RFC, TK, ASK, and OL contributed to the conception and design of the study. NB, DS, MA, JGB, NR, RFC, TK, and ASK contributed to patient data collection/acquisition of data. NB, DS, MA, JGB, NR, RFC, TK, ASK, BF, and OL contributed to the analysis and interpretation of data. All authors contributed to the writing of the manuscript in collaboration with the medical writers and approved the final version for submission.

ORCID

Noa Biran https://orcid.org/0000-0003-0693-4202

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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