Received: 17 April 2020 | Revised: 23 October 2020 | Accepted: 25 October 2020

DOI: 10.1002/ajh.26041

RESEARCH ARTICLE

A phase 1b study of once-weekly carfilzomib combined with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma

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Abstract

Twice-weekly carfilzomib with lenalidomide-dexamethasone (Rd) is an effective regimen for newly diagnosed multiple myeloma (NDMM). Here we evaluated once-weekly carfilzomib with Rd (once-weekly KRd) in NDMM patients. The NDMM patients were enrolled regardless of transplant eligibility. Patients received carfilzomib on days 1, 8, and 15; lenalidomide 25 mg on days 1-21; and dexamethasone 40 mg on carfilzomib days (also day 22 for cycles 1-8) for ≤18, 28-day cycles. Enrollment initiated in a carfilzomib 20/70 mg/m^2 (20 mg/m^2 on cycle one, day 1; 70 mg/m^2 thereafter) NDMM dose-expansion arm, which was suspended because of serious adverse events. After evaluation of dose-limiting toxicities in a two-step-up dose-evaluation cohort, an NDMM dose-expansion arm (carfilzomib 20/56 mg/m^2) was opened. Fifty-one NDMM patients were enrolled in dose-finding and dose-expansion cohorts. Results are presented for the carfilzomib 56 mg/m^2 NDMM dose-expansion arm (n = 33). The grade ≥ 3 treatment-emergent AE (TEAE) rate was 63.6%. Twenty-five patients underwent stem cell collection; 18 proceeded to auto stem cell transplant, and five resumed KRd on study after autoSCT. The overall response rate (ORR) based on best overall response by cycle four was 97.0% (≥very good partial response [VGPR], 69.7%) in the NDMM 20/56 mg/m^2 cohort. In patients who did not receive autoSCT (n = 15), the median number of cycles was 16.0; ORR was 93.3% (≥VGPR, 80.0%). At a median follow-up of 8.1 months, median progression-free survival was not reached. Once-weekly KRd (carfilzomib 56 mg/m^2) had a favorable safety profile and promising activity in NDMM, supporting the use of this regimen in this setting.

1 | INTRODUCTION

Triplet combination regimens consisting of a proteasome inhibitor, an immunomodulatory agent, and dexamethasone are among the most active treatment options for patients with newly diagnosed multiple myeloma (NDMM). Triplet combination strategies have been associated with deep responses,[1-5] and randomized, phase three trials have demonstrated prolonged progression-free survival (PFS) with triplet

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regimens vs doublets in NDMM.[1,2] The combination of the first-in-class proteasome inhibitor bortezomib with lenalidomide and dexamethasone (Rd) is considered a preferred regimen for transplant-eligible and transplant-ineligible patients with NDMM by the National Comprehensive Cancer Network (NCCN),[6] based on data from the SWOG S0777 study that showed that the addition of bortezomib to Rd (VRd) extended PFS and OS in patients with NDMM.[2] Triplet therapies are also preferred for NDMM treatment in Europe.[7] Evaluation of frontline triplet combination regimens incorporating other proteasome inhibitors has been a focus of recent studies; however, carfilzomib-containing triplets have not yet been approved for NDMM in either the US or Europe.[4,8-13]

Carfilzomib is a selective, irreversible, second-generation proteasome inhibitor that is administered as an intravenous infusion. Twice-weekly carfilzomib in combination with Rd (twice-weekly KRd) has been evaluated in the frontline setting. The regimen is included as a recommended regimen (category 2A) by the NCCN (2.2020) for the treatment of transplant-eligible and transplant-ineligible patients with NDMM. The recommendation by the NCCN was based on data from three trials of twice-weekly KRd. A phase one/two study (N = 53) from the Multiple Myeloma Research Consortium (MMRC) showed that treatment with twice-weekly KRd (carfilzomib at 20, 27, or 36 mg/m^2) resulted in a very good partial response (VGPR) or better rate of 81% and a near complete response (CR) or better rate of 62% in transplant-eligible and transplant-ineligible patients with NDMM.[3] A phase two study (N = 45) of frontline twice-weekly KRd (carfilzomib at 36 mg/m^2) showed similar response rates as the MMRC study (≥VGPR, 89%; ≥near CR, 62%) in patients with NDMM (patients were enrolled regardless of transplant eligibility).[5] Another phase two study (N = 76) from the MMRC showed that twice-weekly KRd (carfilzomib at 36 mg/m^2) plus autologous stem cell transplantation (autoSCT) yielded deep responses (≥VGPR, 91%; stringent CR [sCR], 75%) in transplant-eligible patients with NDMM; 72 of 76 patients had completed autoSCT.[4]

Although twice-weekly KRd has been shown to be an active regimen in the frontline setting, a once-weekly infusion schedule would be more convenient. Improved convenience and efficacy were reported with once-weekly carfilzomib (70 mg/m^2) and dexamethasone compared with twice-weekly carfilzomib (27 mg/m^2) and dexamethasone in the phase three A.R.R.O.W. study.[14,15] Therefore, we conducted a phase 1b study exploring the feasibility of once-weekly carfilzomib in combination with Rd (once-weekly KRd) in patients with relapsed/refractory multiple myeloma (RRMM) and NDMM. Results for patients with RRMM were recently reported, and they showed that once-weekly KRd dosing was well tolerated in the relapsed/refractory setting.[16] Here, we report the phase 1b study results from patients with NDMM who received once-weekly KRd at carfilzomib 56 mg/m^2. The primary objective was evaluation of safety and tolerability of once-weekly KRd; efficacy was a secondary objective. Patients were eligible regardless of transplant eligibility. Under the original protocol, patient study participation ended at time of transplant, and an amendment allowed patients to remain on trial and resume KRd after transplant.

2 | METHODS

2.1 | Study design and participants

This was an open-label, phase 1b study of once-weekly KRd conducted in the United States (US) (NCT02335983). The study explored this regimen in patients with RRMM (dose-evaluation cohorts one to three; dose-expansion arm two) and NDMM (dose-evaluation cohort four; dose-expansion arms one and three) (Figure 1)[16]; here we report results for the NDMM group. Patients with NDMM were initially enrolled for treatment with carfilzomib at 20/70 mg/m^2 (20 mg/m^2 on day 1 of cycle one; 70 mg/m^2 thereafter) in a dose-expansion arm (arm one, Figure 1). After serious adverse events (AEs) occurred in cycle one for two of the first patients with NDMM, enrollment in arm one was suspended. A subsequent protocol amendment specified that an NDMM dose-evaluation cohort (cohort four; Figure 1) would be added to evaluate a two-step-up carfilzomib dosing schedule (20 mg/m^2 on day 1 of cycle one; 56 mg/m^2 on days 8 and 15 of cycle one; 70 mg/m^2 thereafter). On evaluation of the dose-limiting toxicity (DLT) data from cohort four, the cohort safety review committee (CSRC) elected to open an NDMM dose-expansion arm (arm three, Figure 1) at carfilzomib 20/56 mg/m^2 (20 mg/m^2 on day 1 of cycle one; 56 mg/m^2 thereafter).

Patients with NDMM were eligible if they had multiple myeloma (MM) and no prior treatment for the disease; they were eligible regardless of transplant eligibility or plan. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0-2, left ventricular ejection fraction of ≥40%, and creatinine clearance of ≥50 mL/min within 21 days before cycle one, day 1. Patients with NDMM were excluded if they had IgM MM; active congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, uncontrolled conduction abnormalities, acute diffuse infiltrative pulmonary disease, pericardial disease, or myocardial infarction within 6 months before cycle one, day 1; active infection within 14 days before cycle one, day 1, requiring systemic antibiotics; uncontrolled hypertension; or grade ≥ 3 neuropathy within 14 days before cycle one, day 1.

The study was conducted in accordance with the protocol, which was approved by the Institutional Review Board or Independent Ethics Committee of all participating institutions prior to enrollment. All patients provided written, informed consent.

2.2 | Treatment

Once-weekly KRd was administered in 28-day cycles for up to 18 cycles. Interruption of KRd therapy after cycle four for stem cell collection, or stem cell collection followed by conditioning and autoSCT, was permitted. Patients were allowed to resume weekly KRd on study protocol, if restarted within 100 days of autoSCT. Carfilzomib was administered once-weekly intravenously (IV) over 30 minutes on days 1, 8, and 15. Oral lenalidomide

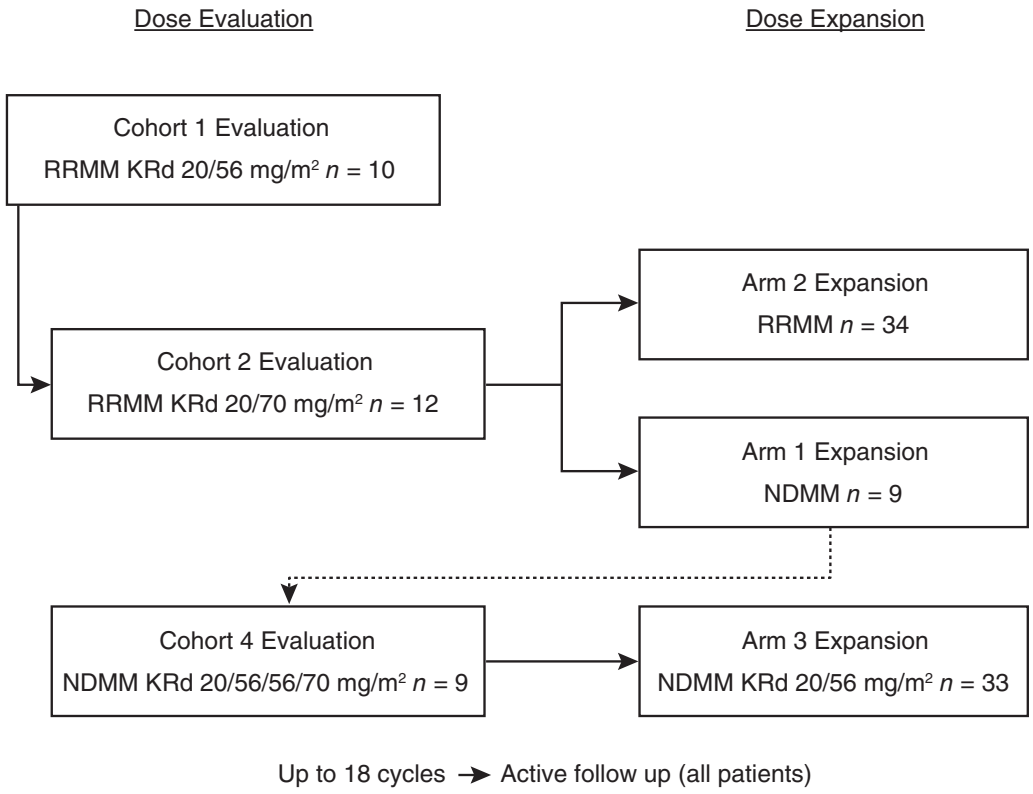

FIGURE 1 Study schema (KRd, carfilzomib, lenalidomide, and dexamethasone. NDMM, newly diagnosed multiple myeloma; RRMM, relapsed or refractory multiple myeloma). Optional cohort three was not opened

(25 mg) was administered on days 1-21. Dexamethasone (40 mg; oral or IV) was administered on days 1, 8, 15, and 22 for cycles one to eight with day 22 omitted for cycles nine and beyond. In the 70 mg/m^2 NDMM dose-expansion arm, carfilzomib was given at a dose of 20 mg/m^2 on day 1 of cycle one and then escalated to 70 mg/m^2 for all subsequent dosing days. In the two-step-up NDMM dose-evaluation arm, carfilzomib was given at a dose of 20 mg/m^2 on day 1 of cycle one, 56 mg/m^2 on days 8 and 15 of cycle one, and 70 mg/m^2 on all subsequent dosing days. In the 56 mg/m^2 NDMM dose-expansion arm, carfilzomib was given at a dose of 20 mg/m^2 on day 1 of cycle one and then escalated to 56 mg/m^2 for all subsequent dosing days. Required concomitant medications included antiviral and thromboembolic prophylaxis. With regard to thromboembolic prophylaxis, aspirin (or another anticoagulant/antiplatelet medication such as clopidogrel bisulfate [INN clopidogrel], low molecular weight heparin, or warfarin) was a required concomitant medication while taking lenalidomide. Low molecular-weight heparin or therapeutic doses of warfarin were required in patients with a prior history of deep vein thrombosis. Once-daily enteric-coated aspirin at the standard prophylactic dose was administered orally for the duration of lenalidomide treatment. Patients with known high thrombotic risk received full anticoagulation at the investigator's discretion. Note, IV hydration (250-500 mL normal saline or appropriate fluid) was given before each carfilzomib infusion during cycle one.

2.3 | Assessments

The primary objective of the study was to assess the safety and tolerability of once-weekly KRd. Primary endpoints included the type, incidence, and severity of AEs. Treatment-emergent AEs (TEAEs) were summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Additionally, AEs of interest, including cardiac failure and acute renal failure, were summarized with Standardized MedDRA Query Narrow (SMQN) terms. Patients were monitored for AEs from the time of informed consent through 30 days after receiving the last dose of study drugs. Definitions for DLTs have been previously described.[16]

The efficacy of once-weekly KRd was assessed as a secondary objective. Secondary endpoints included ORR (defined as the proportion of patients with a partial response or better), the proportion of patients with a CR or better, and PFS. Responses were determined by investigators according to disease assessments (laboratory, bone marrow aspirate, and imaging evaluations) and criteria from the International Myeloma Working Group-Uniform Response Criteria.[17,18] Disease assessments were performed at screening, day 1 of cycle two, and on day 1 (±3 days) for cycles 3-18. Bone marrow aspirates were collected at baseline, on cycle eight, day 1 (±3 days), and to confirm CR or sCR. The protocol required testing for minimum residual

disease by flow cytometry and next generation sequencing at cycle eight and on achieving a CR. Safety and efficacy analyses were performed in patients with NDMM who received at least one dose of carfilzomib.

3 | RESULTS

3.1 | Patients and enrollment

Enrollment of patients with NDMM into the study occurred between March 2016 and October 2017. The final database snapshot date was November 21, 2019. A total of 51 patients with NDMM were enrolled and treated. Nine patients were initially treated in the carfilzomib 70 mg/m^2 NDMM dose-expansion arm. The TEAEs and responses for the NDMM dose-expansion arm are shown in Table S1 and Figure S1, respectively. In this arm, enrollment was discontinued when two serious AEs (grade three thrombotic microangiopathy; grade four thrombotic microangiopathy) were observed during the first cycle. Subsequently, an additional nine patients were treated on the two-step-up KRd dosing schedule in an NDMM evaluation arm (cohort four). The TEAEs and responses for the NDMM evaluation arm are shown in Table S2 and Figure S2, respectively. The CSRC reviewed AE data and recommended enrolling a new NDMM dose-expansion arm at carfilzomib 56 mg/m^2. The recommendation was based on a review of DLT data (four DLTs in nine DLT-evaluable patients: one patient with grade four hypocalcemia and grade three hypomagnesemia in cycle one [patient had hypocalcemia and hypomagnesemia at baseline]; one patient with grade three alanine aminotransferase elevation during cycle one; two patients with grade three rash during cycle two).

Results are presented for the 33 patients who received once-weekly KRd at carfilzomib 56 mg/m^2 in the dose-expansion arm. Patient demographics and baseline disease characteristics for patients who received once-weekly KRd at carfilzomib 56 mg/m^2 are shown in Table 1. The median age was 60.0 years (range, 36-76 years); most patients (69.7%) were aged <65 years. Among patients who did not proceed to transplant, the median age was 64 years (range, 51-76 years). The proportion of patients with high-risk cytogenetic abnormalities was 18.2%. Twenty-four (72.7%) patients treated with once-weekly KRd 56 mg/m^2 underwent autologous stem cell collection and 18 (54.5%) went on to autoSCT after a median of five cycles. Of patients who went on to autoSCT, the median age was 54.0 years (range, 36-72 years). Five patients resumed once-weekly KRd on study after autoSCT; for these five patients, the median time to resuming KRd after autoSCT was 96 days (range, 91-99 days). The remaining 13 patients who underwent autoSCT ended study participation at the time of transplant.

TABLE 1 Patient demographics and baseline disease characteristics

Characteristic	Carfilzomib 56 mg/m^2 (n = 33)
Sex, n (%)	
Male	17 (51.5)
Age	
Median (range), years	60.0 (36–76)
<65 years, n (%)	23 (69.7)
65-74 years, n (%)	9 (27.3)
≥75 years, n (%)	1 (3.0)
ECOG performance status, n (%)	
0	12 (36.4)
1	21 (63.6)
ISS stage at baseline, n (%)	
I	12 (36.4)
II	13 (39.4)
III	4 (12.1)
Unknown	4 (12.1)
Cytogenetic risk group (local laboratory),[a] n (%)	
High	6 (18.2)
Standard	23 (69.7)
Unknown	4 (12.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.
[a]Patients with chromosomal abnormalities t(4;14) [≥10%], t(14;16) [≥10%], and/or del(17p) [≥20%] were included in the high-risk group. Patients with normal cytogenetics or other chromosomal abnormalities were included in the standard-risk group.

3.2 | Treatment exposure and safety

Safety is reported for the 33 patients who received once-weekly KRd at carfilzomib 56 mg/m^2. Adverse event reporting includes findings surrounding autoSCT for those patients who resumed KRd on study after autoSCT. The median dose per administration of carfilzomib was 52.8 mg/m^2 (range, 33.9-56.2 mg/m^2). Nine patients (27.3%) had a dose reduction to 45 mg/m^2; eight of these were due to AEs, and the remaining patient did not have a reason given. One patient discontinued carfilzomib because of TEAEs (blood alkaline phosphatase increased and hyperbilirubinemia). The median number of cycles patients received carfilzomib was 7.0 (range, 1.0-18.0); 30.3% of patients received carfilzomib for 18 cycles. Among patients who did not receive autoSCT, the median number of cycles of carfilzomib was 16.0, and among patients who went on to autoSCT, the median number of cycles of carfilzomib was 5.0.

All patients reported at least one TEAE of any grade. The most common (>2 patients) hematologic TEAEs of any grade were anemia (27.3%) and neutropenia/neutrophil count decreased (12.1%); the most common nonhematologic TEAEs of any grade were insomnia (51.5%), nausea (51.5%), diarrhea (48.5%), upper respiratory tract infection (45.5%), fatigue (39.4%), and headache (39.4%) (Table 2). The patient incidence of grade ≥ 3 TEAEs was 63.6%. The most common (>2 patients) grade ≥ 3 hematologic TEAEs were anemia (15.2%)

TABLE 2 Treatment-emergent adverse events (AEs)[a]

Any-grade AEs in ≥25% of patients or grade ≥ 3 AEs in >1 patient, n (%)	Carfilzomib 56 mg/m^2 (n = 33)	
	Any grade	Grade ≥ 3
Insomnia	17 (51.5)	0
Nausea	17 (51.5)	0
Diarrhea	16 (48.5)	1 (3.0)
Upper respiratory tract infection	15 (45.5)	1 (3.0)
Headache	13 (39.4)	0
Fatigue	13 (39.4)	2 (6.1)
Muscular weakness	12 (36.4)	1 (3.0)
Dizziness	12 (36.4)	0
Cough	12 (36.4)	0
Edema peripheral	11 (33.3)	1 (3.0)
Pruritus	11 (33.3)	0
Constipation	10 (30.3)	0
Dyspnea	10 (30.3)	2 (6.1)
Anemia	9 (27.3)	5 (15.2)
Rash	8 (24.2)	2 (6.1)
Alanine aminotransferase increased	7 (21.2)	3 (9.1)
Hyponatremia	5 (15.2)	4 (12.1)
Dehydration	4 (12.1)	2 (6.1)
Neutropenia[b]	4 (12.1)	3 (9.1)
White blood cell count decreased	4 (12.1)	3 (9.1)
Lymphocyte count decreased	3 (9.1)	2 (6.1)
Platelet count decreased	3 (9.1)	2 (6.1)
Syncope	3 (9.1)	2 (6.1)

[a]AEs reported as preferred term.
[b]Neutropenia included both the preferred terms neutropenia and neutrophil count decreased.

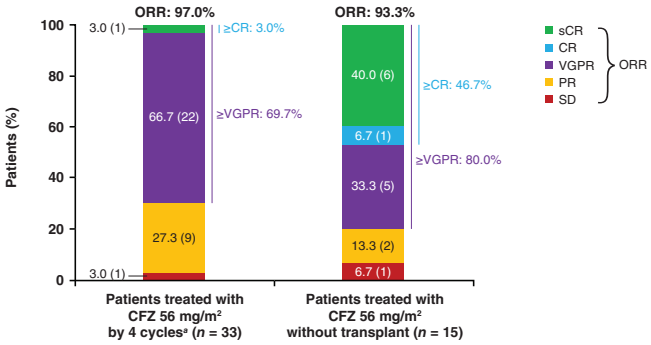

FIGURE 2 Response as determined by investigators. Values in bars correspond to % (n) patients. CFZ, carfilzomib; CR, complete response; ORR, objective response rate; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR.
[a] Excludes responses after stem cell transplant

and neutropenia/neutrophil count decreased (9.1%); the most common (>2 patients) grade ≥ 3 nonhematologic TEAEs were hyponatremia (12.1%) and alanine aminotransferase increased (9.1%) (Table 2). With respect to AEs of interest, no patients were reported to have grade ≥ 3 cardiac failure (SMQN term), one patient (3.0%) was reported to have grade ≥ 3 acute renal failure (SMQN term), and one patient (3.0%) was reported to have grade ≥ 3 venous embolic and thrombotic events (SMQN term). One patient had a grade ≥ 3 infection (upper respiratory tract infection). The patient incidence of serious TEAEs was 33.3%. There were no fatal TEAEs or patient deaths reported for NDMM patients (n = 51) in the study.

3.3 | Efficacy

To evaluate responses to KRd, independent of the effect of high dose therapy with autoSCT rescue, we evaluated the response at cycle four for all patients in the carfilzomib 56 mg/m^2 dose-expansion arm (n = 33). The ORR by cycle four was 97.0% (VGPR or better rate, 69.7%; CR or better rate, 3.0% [one patient achieved sCR]) (Figure 2). The median time to response was 29 days (range, 28-57 days). Responses appeared to deepen with time: among patients who did not receive autoSCT (n = 15), the median duration of treatment for all study drugs was 16.0 cycles, VGPR or better rate was 80.0%, and the CR or better rate was 46.7%. A majority of patients who received autoSCT came off study at the time of autoSCT (13/18), and thus we have limited information on the best overall response in the frontline setting for NDMM patients who received autoSCT. With this limitation in mind, for the 18 patients who received autoSCT, the ORR was 100% (VGPR or better rate, 77.8%; CR or better rate, 22.2% [three patients achieved sCR]) at any time in the study. At median follow-up time of 8.1 months (95% confidence interval, 5.7-16.5 months), median PFS was not reached; one patient had disease progression at the time of data cutoff.

4 | DISCUSSION

Twice-weekly KRd is an active regimen capable of producing deep responses with a favorable safety profile in patients with NDMM. In a previous analysis of the current study, we showed that a more convenient once-weekly schedule of KRd was feasible and active in patients with RRMM and produced similar ORRs as those observed for the twice-weekly KRd regimen.[16] The analysis reported here describes outcomes for NDMM patients treated with weekly KRd in a small study using 56 mg/m^2 weekly in NDMM patients. Consistent with results reported in RRMM,[16] once-weekly KRd (carfilzomib 56 mg/m^2) was active and well tolerated in patients with NDMM.

In this study, patients with NDMM were initially enrolled into a carfilzomib 70 mg/m^2 dose-expansion arm, per protocol, based on dose evaluation in patients with RRMM. After two serious AEs occurred in cycle one for NDMM subjects enrolled in the carfilzomib 70 mg/m^2 dose-expansion arm, as described earlier, and subsequent review of the two-step dose-evaluation arm, the CSRC elected to open a carfilzomib 56 mg/m^2 dose-expansion arm. The once-weekly

KRd regimen with carfilzomib at the 70 mg/m^2 dose was not well tolerated in this study, and should not be administered to patients with NDMM. The observation in NDMM that once-weekly KRd at carfilzomib 56 mg/m^2 was better tolerated than once-weekly KRd at carfilzomib 70 mg/m^2 is consistent with the results reported for the once-weekly KRd regimen in RRMM. Therefore, when using this regimen in patients with NDMM, carfilzomib should be given at the 56 mg/m^2 dose.

In this study, once-weekly KRd at carfilzomib 56 mg/m^2 was well tolerated and had a favorable safety profile in patients with NDMM. Only one patient discontinued carfilzomib because of an AE of elevated alanine aminotransferase in cycle one. No new safety signals were observed relative to the twice-weekly KRd regimen in patients with NDMM or RRMM[3,5,19] and the once-weekly KRd regimen in patients with RRMM.[16] In our study, grade ≥ 3 neutropenia/neutrophil count decrease occurred in 9% of patients with NDMM, and only one patient had a grade ≥ 3 infection. In contrast, rates of grade ≥ 3 neutropenia and infections were > 20% in phase three trials of other combination therapies involving proteasome inhibitors or monoclonal antibodies in NDMM.[20,21]

In this trial, the majority (72.7%) of NDMM patients treated with once-weekly KRd at carfilzomib 56 mg/m^2 underwent stem cell collection; 54.5% went on to autoSCT after a median of five cycles of once-weekly KRd. The ability of most patients to successfully undergo stem cell collection and autoSCT in this study is consistent with previous reports demonstrating that the twice-weekly KRd regimen did not adversely affect collection in patients with NDMM.[3,5] These previous studies evaluated twice-weekly KRd at carfilzomib 36 mg/m^2. Our study demonstrates that stem cell collection and autoSCT were feasible after treatment with once-weekly KRd at carfilzomib at 56 mg/m^2.

Once-weekly KRd at carfilzomib 56 mg/m^2 showed promising efficacy in patients with NDMM. The rates of response as reported here for this early phase trial reflect the response to the triplet therapy, independent of the effects of conditioning and autoSCT, and are based on small patient numbers. Outcomes were not compared between high-risk and standard-risk patients because of sample size limitations. To study the efficacy of the once-weekly KRd triplet, response rates for patients in the carfilzomib 56 mg/m^2 dose-expansion arm (n = 33) were reported according to best overall responses achieved by cycle four (to exclude post-autoSCT responses), and response rates for patients who did not receive autoSCT were presented separately. In a previous study of twice-weekly KRd in NDMM, which allowed patients to proceed to autoSCT, the sCR rate at the end of four cycles was 6% and increased to 61% among patients who received eight or more cycles, suggesting that extended treatment with KRd is needed to attain the deepest levels of response.[3] The weekly KRd study reported here was not originally designed to include autoSCT, resulting in a short median follow-up due to a large proportion of study participants ending study at the time of autoSCT.

The response rates achieved with once-weekly KRd by cycle four (n = 33; ORR, 97.0%; ≥VGPR, 69.7%; ≥CR, 3.0%) and during the course of the study for patients who did not receive autoSCT (n = 15; ORR, 93.3%; ≥VGPR, 80.0%; ≥CR, 46.7%) are similar to those observed for frontline regimens considered preferred options by the NCCN, including VRd and cyclophosphamide, bortezomib, and dexamethasone (CyBorD).[2,22-25]

The ORRs and rates of ≥VGPR for once-weekly KRd are also similar to those of recently investigated frontline regimens, including twice-weekly ixazomib with Rd (twice-weekly IRd) in transplant-eligible or transplant-ineligible patients,[12] once-weekly IRd followed by ixazomib maintenance in transplant-eligible or transplant-ineligible patients,[9,11] daratumumab plus Rd in transplant-ineligible patients,[20] daratumumab plus VTd in transplant-eligible patients,[21] and twice-weekly KRd.[3-5,8,26] In studies investigating twice-weekly KRd, the ≥VGPR rate ranged from 81% to 91% per ITT analysis; the majority of these patients in these studies had received eight or more cycles of twice-weekly KRd).[3-5,8,26] In the large randomized FORTE trial, pre-maintenance rates of ≥ CR and ≥ VGPR were approximately 50% and 87%, respectively, for twice-weekly KRd administered with or without ASCT for transplant-eligible patients with NDMM.[8]

In our analysis, median PFS was not reached at a median follow-up time of 8.1 months. In the recent phase 3 ENDURANCE trial of induction therapy for NDMM in standard or intermediate risk, transplant-ineligible or transplant-deferred patients, twice-weekly KRd administered for nine cycles did not improve median PFS vs VRd (34.6 months vs 34.4 months; HR, 1.04 [95% CI, 0.8-1.3]).[27] Further studies are needed to evaluate whether once-weekly KRd could improve outcomes vs twice-weekly KRd or VRd.

In conclusion, once-weekly carfilzomib at 56 mg/m^2 in combination with Rd has a favorable safety profile and showed promising anti-MM efficacy in patients with NDMM, and this dose will be investigated in future clinical studies. An ongoing phase three study (NCT03859427) is evaluating once-weekly KRd at carfilzomib 56 mg/m^2 vs twice-weekly KRd at carfilzomib 27 mg/m^2 in patients with RRMM with a primary endpoint of ORR. Although not powered for efficacy, rates of overall response and ≥ VGPR reported in this study were similar to those of other frontline KRd studies. These results support the use of once-weekly KRd regimen in patients with NDMM.

ACKNOWLEDGMENTS

This study was supported by Amgen Inc. Medical writing assistance was provided by Andrew Gomes, PhD, of BlueMomentum, an Ashfield Company, part of UDG Healthcare plc, and funded by Amgen Inc. Dr. Landgren is supported by the Memorial Sloan Kettering Core Grant (P30 CA008748).

CONFLICT OF INTEREST

Melissa Alsina: Honoraria from Janssen, Amgen, and Celgene; consulting or advisory role fees for Celgene and BMS; speakers' bureau participation for Janssen and Amgen; and research funding from BMS. Ola Landgren: Research funding from National Institutes of Health, US Food and Drug Administration, Multiple Myeloma Research Foundation, International Myeloma Foundation, Leukemia and Lymphoma Society, Perelman Family Foundation, Rising Tides Foundation,

Amgen, Celgene, Janssen, Takeda, Glenmark, Seattle Genetics, and Karyopharm; honoraria/advisory boards for Adaptive, Amgen, Binding Site, BMS, Celgene, Cellectis, Glenmark, Janssen, Juno, Pfizer; Independent Data Monitoring Committees for clinical trials led by Takeda, Merck, Janssen. Noopur Raje: Consulting or advisory role fees for Amgen, Novartis, Takeda, Celgene, and Bluebird; and research funding from AstraZeneca and Eli Lilly. Ruben Niesvizky: Honoraria for speakers' bureau activities, advisory board membership, and research funding from Celgene Inc, Takeda Inc, and Onyx Inc. William I. Bensinger: Honoraria from Celgene, Amgen, and Takeda; consultancy/advisory role from Celgene, Sanofi, and BMS; research funding from Celgene, Sanofi, Acetylon, BMS, and Takeda; speakers' bureau of Celgene, Amgen, and Takeda; and expert testimony from Celgene and Takeda. Jesus G. Berdeja: Research funding from Abbvie, Amgen, Bluebird, BMS, Celgene, Genentech, Glenmark, Janssen, Novartis, Poseida, Sanofi, Takeda, and Teva; consulting fees from Takeda, BMS, Karyopharm, CRISPR Therapeutics, Celgene, Kite Pharma Inc, and Servier. Tibor Kovacsovics: Research support from Abbvie and Amgen, and consulting fees from Amgen and Celgene. David H. Vesole: No disclosures reported. Belle Fang: Employed by Amgen. Amy S. Kimball: Employed by Amgen; stock or other ownership with Amgen, and stock ownership in WindMIL Therapeutics. David S. Siegel: Honoraria and consulting or advisory role fees for Celgene, Amgen, Merck, Janssen, BMS, Takeda, and Karyopharm; speakers' bureau participation for Celgene, Amgen, Merck, Janssen, BMS, and Takeda; and research funding from Celgene.

AUTHOR CONTRIBUTIONS

All authors played a role in the interpretation and analysis of data, in drafting the manuscript, and in the decision to submit the manuscript for publication.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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

How to cite this article: Alsina M, Landgren O, Raje N, et al. A phase 1b study of once-weekly carfilzomib combined with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma. *Am J Hematol*. 2021;96:226–233. https://doi.org/10.1002/ajh.26041