Original Article

Carfilzomib, Bendamustine, and Dexamethasone in Patients With Advanced Multiple Myeloma: The EMN09 Phase 1/2 Study of the European Myeloma Network

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BACKGROUND: Combined therapy with carfilzomib, bendamustine, and dexamethasone was evaluated in this multicenter phase 1/2 trial conducted within the European Myeloma Network (EMN09 trial). **METHODS:** Sixty-three patients with relapsed/refractory multiple myeloma who had received ≥2 lines of prior therapy were included. The phase 1 portion of the study determined the maximum tolerated dose of carfilzomib with bendamustine set at 70 mg/m^2 on days 1 and 8. After 8 cycles, responding patients received maintenance therapy with carfilzomib and dexamethasone until progression. **RESULTS:** On the basis of the phase 1 results, the recommended phase 2 dose for carfilzomib was 27 mg/m^2 twice weekly in weeks 1, 2, and 3. Fifty-two percent of patients achieved a partial response or better, and 32% reached a very good partial response or better. The clinical benefit rate was 93%. After a median follow-up of 21.9 months, the median progression-free survival was 11.6 months, and the median overall survival was 30.4 months. The reported grade ≥3 hematologic adverse events (AEs) were lymphopenia (29%), neutropenia (25%), and thrombocytopenia (22%). The main nonhematologic grade ≥3 AEs were pneumonia, thromboembolic events (10%), cardiac AEs (8%), and hypertension (2%). **CONCLUSIONS:** In heavily pretreated patients who have relapsed/refractory multiple myeloma, combined carfilzomib, bendamustine, and dexamethasone is an effective treatment option administered in the outpatient setting. Infection prophylaxis and attention to patients with cardiovascular predisposition are required. ***Cancer* 2021;127:3413-3421**.

KEYWORDS: bendamustine, carfilzomib, multiple myeloma, phase 1/2 study.

INTRODUCTION

The survival of patients with multiple myeloma (MM) increased in the past 2 decades, with many patients now reaching an overall survival (OS) of 10 years.[1] Despite recently introduced immunotherapeutic strategies, MM remains most often incurable, and options are needed for patients who relapse after the first-generation novel agents bortezomib, lenalidomide, and thalidomide. The recently introduced second-generation irreversible proteasome inhibitor (PI) carfilzomib was effective even in patients who were previously exposed and refractory to bortezomib and did not lead to peripheral neuropathy (PN) because of minimal off-target activity against nonproteasomal proteases.[2-4] The drug was initially approved in combination with lenalidomide plus dexamethasone for relapsed and/or refractory MM (RRMM)[8] and was approved later at a different dose combined with dexamethasone alone.[5] These data provide the rationale to combine carfilzomib plus dexamethasone with other agents.

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Bendamustine, a bifunctional N-Lost derivate, has structural similarities to alkylating agents and antimetabolites.[6] In MM, bendamustine plus prednisone was superior to melphalan plus prednisone regarding the complete response (CR) rate, the time to treatment failure, and quality of life.[7] Bortezomib may act synergistically with alkylating agents by increasing apoptosis induced by a PI because of an accumulation of defective ribosomal products or by inhibition of DNA repair.[8-10] Although bortezomib-induced PN was an issue, bendamustine combined with bortezomib showed promising activity in patients with advanced MM.[11-13] Bendamustine is currently approved in Europe even for patients who have MM with severe renal insufficiency.

Carfilzomib is well tolerated in patients with RRMM and is an option in bortezomib-refractory patients with existing PN.[14-16] Bendamustine produces little emesis or hair loss.[11,12] Both drugs can be given combined in an outpatient setting, and bendamustine is particularly appealing because many patients with advanced MM have received little chemotherapy. Yet, given the increased use of continuous lenalidomide therapy upfront, novel immunomodulatory drug (IMiD)-free options are needed that are effective in patients who previously received bortezomib. This multicenter, open-label, dose-escalation phase 1/2 study was conducted within the European Myeloma Network as EMN09 to determine the maximum tolerated dose (MTD), the safety, and the efficacy of combined carfilzomib, bendamustine, and dexamethasone (KBd) in patients with RRMM.

MATERIALS AND METHODS

Patients with RRMM who had received ≥2 prior lines of therapy were included. Eligibility criteria were measurable disease, Karnofsky performance status ≥60%, creatinine clearance ≥15 mL per minute, platelet count ≥70×10^9/L (≥50×10^9/L if MM involvement in the bone marrow was >50%), and neutrophil count ≥1×10^9/L. Major exclusion criteria were grade >2 PN, active infection with hepatitis type B, C, or HIV positivity, and as congestive heart failure (New York Heart Association class >II). Patients received electrocardiogram and echocardiographic evaluations and were excluded if they had a left ventricular ejection fraction <40%, symptomatic ischemia, or uncontrolled grade ≥3 conduction system abnormalities. All patients provided written informed consent to participate in the study, which had been approved by the institutional ethics committees. The study was conducted with the principles of Good Clinical Practice in accordance with the Declaration of Helsinki and was registered as ClinicalTrials.gov NCT02056756 and EudraCT number 2012-003938-17.

The primary objective of the phase 1 portion was to determine the MTD of KBd, and the primary objective of the phase 2 portion was to determine the rate of very good partial responses (VGPRs). Secondary end points included overall response rates, progression-free survival (PFS), OS, and subgroup analyses of prognostic factors. Response was assessed according to the International Myeloma Working Group criteria with the addition of a near-complete response (nCR).[17]

All patients received oral dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23. After intravenous prehydration in the range from 250 to 500 mL, carfilzomib was administered intravenously over 30 minutes on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. In the phase 1 portion, the starting dose of carfilzomib was 27 mg/m^2 (on cycle 1, day 1 and 2 patients received only 20 mg/m^2) (dose level 0). The subsequent carfilzomib doses were planned at 36 mg/m^2 (dose level +1) and 45 mg/m^2 (dose level +2) (see Supporting Fig. 2). Bendamustine was administered intravenously with a 70 mg/m^2 fixed dose on days 1 and 8 of a 28-day cycle. In the phase 2 portion, patients received KBd at the MTD. Treatment was given for 8 cycles, followed by maintenance with carfilzomib at the MTD on days 1, 2, 15, and 16 plus dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 every 28 days until patients developed either progressive disease (PD) or intolerance (see Supporting Fig. 1).

Dose-limiting toxicities (DLTs) according to the National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE version 4.0.) were defined as: any nonhematologic toxicities grade ≥3, except nausea or vomiting responsive to symptomatic therapy, grade 4 neutropenia ≥7 days, other grade 4 hematologic toxicities, febrile neutropenia (defined as grade 3 and 4 neutropenia with fever 38.5 °C), and/or infection requiring antibiotic or antifungal treatment. Initially, lymphopenia was considered a DLT, but this was amended after phase 1, and mandatory infectious prophylaxis was incorporated into the protocol. Assessment of the MTD was performed after completion of the second cycle and was defined as the dose level at which DLT was observed in one-third of patients (see Supporting Fig. 3). Evaluation details and statistical considerations are provided in the Supporting Methods.

RESULTS

Patient Characteristics

Patients with RRMM were enrolled from April 2014 to February 2017 at 7 EMN centers in Italy and in Germany. Thirteen patients were included in the phase 1

TABLE 1. Patient Characteristics

Characteristic	No. of Patients (%)
Age, y	
Median [range], y	66 [37-79]
≤65	27 (43)
>65	36 (57)
Sex	
Men	37 (59)
Women	26 (41)
International Staging System	
I	33 (52)
II	19 (30)
III	11 (17)
mFISH[a]	
High risk[b]	22 (48)
Standard risk	24 (52)
Performance status	
0	26 (41)
≥1	35 (56)
Not available	2 (3)
Disease status	
Primary refractory	3 (5)
Relapsed	41 (65)
Relapsed and refractory	19 (30)
Time from diagnosis to study entry: Median [IQR], y	5.2 [2.7-8.2]
No. of previous lines of therapy, median = 3	
2	24 (38)
3	10 (16)
4	10 (16)
≥5	19 (30)
Previous therapy	
ASCT	47 (75)
Refractory[c]	10 (21)
Bortezomib	55 (87)
Refractory[c]	18 (33)
Immunomodulators[d]	54 (86)
Lenalidomide	48 (76)
Refractory[c]	29 (60)

Abbreviations: ASCT, autologous stem cell transplantation; IQR, interquartile range; mFISH, multicolor fluorescent in situ hybridization.
[a]Values indicate the proportion of patients who had available FISH data (n = 46).
[b]High-risk disease includes deletion 17p [del(17p)], or translocation (4;14) [t(4;14)], or translocation (14;16) [t(14;16)].
[c]The proportions of those with refractory disease were based on the number of patients who received the drug.
[d]Seventeen patients received pomalidomide.

dose-escalation portion of the study, and 50 patients were included in the phase 2 portion. Baseline demographics and disease characteristics are listed in Table 1 and illustrated in Supporting Figure 3. Patients were enrolled a median of 5.2 years after diagnosis and had received a median of 3 prior lines of therapy. Previous treatment was extensive: 75% had received autologous and 13% had received allogeneic hematopoietic stem-cell transplantation, 87% were exposed to a PI, and 86% were exposed to IMiDs (76% had received lenalidomide [60% of these patients were refractory], and 27% had received pomalidomide). None of the patients had received prior carfilzomib or prior CD38 monoclonal antibody treatment. The median age of the entire population was 66 years (range, 37-79 years). Of note, 48% of evaluable patients had an unfavorable chromosomal profile, with t(4;14), del17p, or t(14;16). At data cutoff, all patients were evaluable for safety and response. At a median follow-up of 21.9 months (interquartile range, 16.6-28.2 months), the median duration of treatment was 6.9 months (interquartile range, 4.5-12.4 months). Forty patients went off study during or after induction; the main reason was PD in 20 patients and adverse events (AEs) in 13 patients. Of the 23 patients who proceeded to maintenance therapy, 19 went off protocol mainly because of PD, and 3 patients experienced AEs (see Supporting Fig. 3).

Phase 1 Portion

At dose level 0 (see Supporting Fig. 2), KBd was tolerated and effective. However, 3 of 6 patients experienced grade 4 lymphopenia. The best responses were 2 stringent CRs, 1 nCR, 2 partial responses (PRs), and 1 stable disease. In the absence of other significant toxicities and after discussion with the Independent Data Safety Monitoring Committee, the protocol was amended, and grade 4 lymphopenia was not considered a DLT. At dose level +1, with the carfilzomib dose increased to 36 mg/m^2, 1 in 3 patients experienced grade 4 thrombocytopenia and grade 3 febrile neutropenia. Therefore, 3 additional patients were enrolled at dose level +1; 1 patient experienced PD after cycle 1 and went off study before being evaluated for the occurrence of DLTs (evaluation was planned during the first 2 cycles), so 1 additional patient was included at this dose level. In 1 patient, pneumonia classified as grade 3 was noted. The MTD was then defined at dose level +1. With better tolerability and seemingly equal clinical efficacy, phase 2 was conducted at dose level 0, leading to a total of 50 patients treated at this dose level (see Supporting Fig. 3).

Efficacy

Fifty-six of the 63 patients responded by a decrease in M protein (Fig. 1). In an intention-to-treat analysis, 52% of patients had at least a PR (≥PR), 32% had at least a VGPR (≥VGPR), and 17% had a CR or an nCR (Table 2). Among the 23 patients who responded and were eligible to receive maintenance treatment on 2 consecutive days with carfilzomib and dexamethasone, the ≥VGPR rate was 61%, and the ≥nCR rate was 35%.

The median PFS was 11.6 months (95% CI, 7.9-15.3 months) (Fig. 2A), and the median OS was 30.4 months (95% CI, 20.5 months to not reached) (Fig. 2B). The PFS was significantly better for patients who had standard-risk chromosomal abnormalities compared with those who had

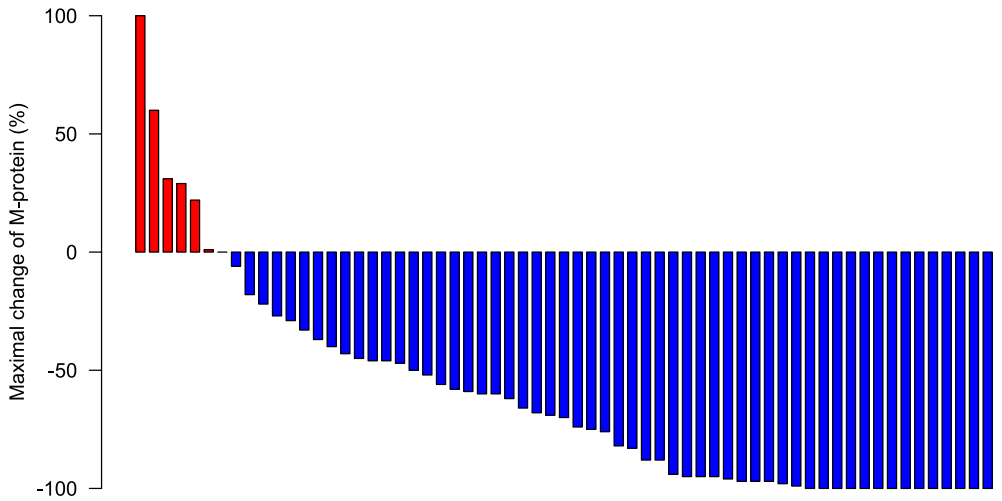

Figure 1. Changes in M-protein levels compared with baseline are illustrated in individual patients with multiple myeloma.

TABLE 2. Best Overall Response, N = 63

Response	No. of Patients (%)
CR	3 (5)
nCR	8 (13)
VGPR	9 (14)
≥VGPR	20 (32)
PR	13 (21)
≥PR	33 (52)
SD	24 (38)
PD	6 (10)

Abbreviations: CR, complete response; nCR, near complete response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

high-risk characteristics (median, 19.6 vs 7.9 months; hazard ratio, 0.43; 95% CI, 0.21-0.88; $P = .021$). Although the subgroup analysis was limited by the small sample size, patients who had a poor prognosis with deletion 17p (n = 14) still reached a PFS of 9.4 months. Similarly, OS was significantly improved in patients who had standard-risk chromosomal abnormalities (18-month OS, 87% vs 52%; hazard ratio, 0.24; 95% CI, 0.08-0.67; $P = .007$) (Fig. 3). No significant differences in PFS were observed between patients who relapsed on or were refractory to lenalidomide (see Supporting Fig. 4A) and those who relapsed on or were refractory to bortezomib (see Supporting Fig. 4B).

Safety

The relevant side effects of KBd protocol are listed in Table 3. Most of the toxicities occurred during induction and were grade 1 or 2. The most common grade 3 and 4 toxicities during induction were hematologic, namely, lymphopenia, neutropenia, thrombocytopenia, and anemia. Twenty-seven percent of patients received granulocyte colony-stimulating factor at some point. Regarding grade 3 and 4 nonhematologic toxicities/serious AEs during induction, the most frequent were infections, mainly pneumonia (13%), which are common in patients with such advanced disease. Six patients developed venous thromboembolism (5 patients developed pulmonary embolisms, and 1 patient developed deep vein thrombosis), including 2 who had a prior history of thromboembolic events. Furthermore, 1 patient developed hypertension (2%), 2 had acute coronary syndrome, and 2 had atrial fibrillation (3%). Three patients died, including 2 who died of heart failure and 1 with prior grade 3 atrial fibrillation who had a sudden death. Overall, 5 of 63 patients had grade ≥3 cardiac events/hypertension, and 4 of them had a prior medical history positive for cardiac events/hypertension.

During maintenance, most AEs were grade 1 or 2. The most frequent grade ≥3 toxicities were hematologic.

Overall, 19 of 63 patients required dose reductions during treatment. In 9 patients, the carfilzomib dose had to be reduced because of cardiovascular toxicity in 3 patients, infections in 2 patients, hematologic toxicity in 2 patients, hepatic toxicity in 1 patient, and constitutional symptoms in 1 patient. The reasons for dexamethasone dose reductions were hyperglycemia, constitutional symptoms, and sleeping problems in 2 patients each; and hematologic or cardiovascular toxicity or infection in 1 patient each. Only 1 patient required a bendamustine dose reduction because of hematologic toxicity.

Thirteen patients required treatment discontinuation for AEs during the induction phase. Cardiovascular AEs occurred in 6 patients, infections and hematologic

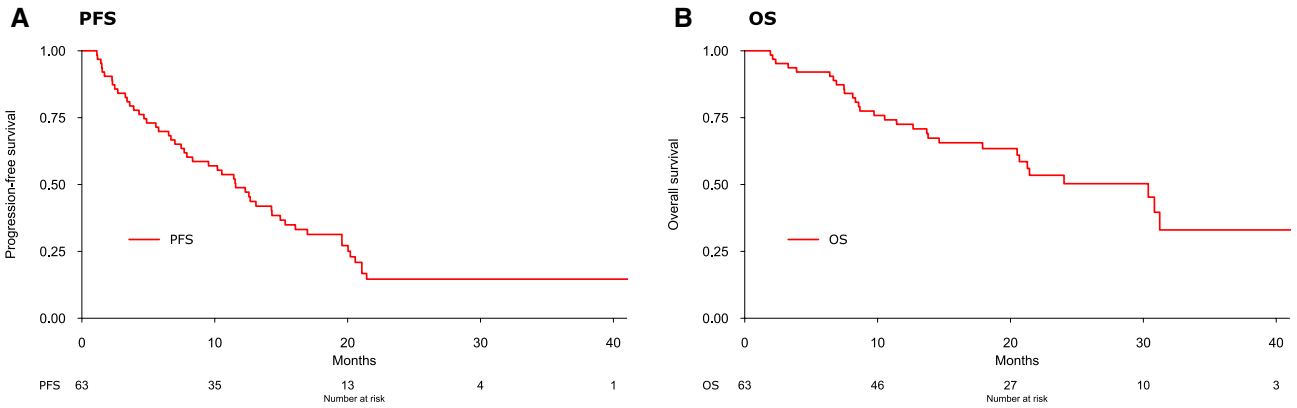

Figure 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) are illustrated in the overall population of enrolled patients.

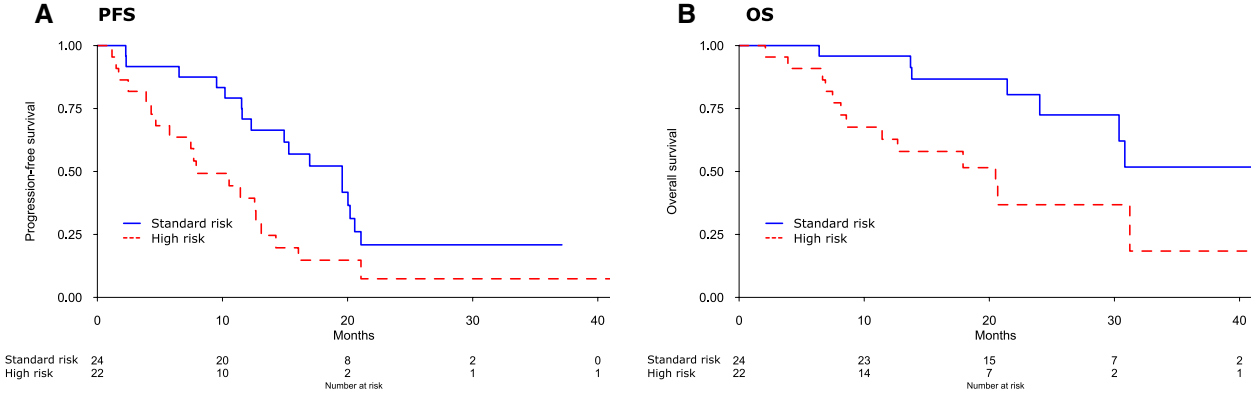

Figure 3. (A) Progression-free survival and (B) overall survival are illustrated in patients with standard-risk versus high-risk multiple myeloma according to chromosomal abnormalities.

toxicity occurred in 2 patients each, and hemorrhagic event and seizure occurred in 1 patient each. Only 3 patients discontinued for AEs during maintenance (pulmonary problems, infection, or hematologic toxicity).

DISCUSSION

In recent years, the treatment armamentarium for patients with RRMM has increased. First-line treatments for both transplantation-eligible and transplantation-ineligible patients now often contain bortezomib and/or lenalidomide and may already include monoclonal antibodies. If not given as first-line treatment, these regimens are then frequently administered as second-line treatment. Therefore, most patients with MM in the first-line or second-line setting have been exposed or are refractory to IMIDs, PIs, and monoclonal antibodies. Because lenalidomide is commonly given until progression, effective treatment of IMiD-refractory patients is currently difficult. In addition, toxicities developed with prior therapies are generally an issue at the time of relapse. One of the most frequent side effects related to bortezomib is PN.[18] The new PI carfilzomib avoids additional PN[2] and proved to be efficient in patients who relapsed on or were relapsed/refractory to bortezomib or lenalidomide.[2,5] Even in later disease stages, patients may not have been exposed to much conventional chemotherapy. A randomized study recently demonstrated a trend toward better PFS when cyclophosphamide was added to carfilzomib and dexamethasone.[19] Bendamustine may be considered because it is well tolerated, induces high rates of DNA double-strand breaks, and has documented activity in MM.[11,12] In vitro, a combination of PI and chemotherapy creates synergistic effects.[8,10] A phase 3 study in patients with untreated

TABLE 3. Main Types of Treatment-Related Adverse Events

	No. of Events (%)				
	Induction, n = 63			Maintenance, n = 23	
Category	Grade 1-2	Grade 3-4 and SAE	Grade 5	Grade 1-2	Grade 3-4 and SAE
Hematologic					
Lymphocytopenia	—	18 (29)[a]	—	1 (4)	4 (17)
Neutropenia	4 (6)	16 (25)	—	1 (4)	1 (4)
Thrombocytopenia	9 (14)	14 (22) [a]	—	1 (4)	1 (4)
Anemia	11 (17)	11 (17)	—	—	—
Infections					
Pneumonia	—	8 (13)[b]	—	—	—
Upper respiratory tract infection	12 (19)	—	—	2 (9)	—
Bronchial infection	5 (8)	—	—	—	—
Genitourinary tract infection	4 (6)	—	—	2 (9)	—
CMV retinitis	—	—	—		1 (4)
Vascular					
Pulmonary embolism	—	5 (8)	—	—	—
Deep vein thrombosis	2 (3)	1 (2)	—	—	—
Hypertension	1 (2)	1 (2)	—	2 (9)	—
Edema	8 (13)	—	—	—	—
Cardiologic					
Heart failure	—	—	2 (3)	—	—
Acute coronary syndrome	—	2 (3)	—	—	—
Atrial fibrillation	1 (2)	2 (3)	—	1 (4)	—
Tachycardia	4 (6)	—	—	—	—
Neurologic					
Seizures	—	2 (3)	—	—	—
Peripheral sensory neuropathy	3 (5)	—	—	4 (17)	—
Tremor	3 (5)	—	—	—	—
Dizziness	6 (10)	—	—	—	—
Myopathy	2 (3)	1 (2)	—	—	—
Dermatologic					
Spinocellular carcinoma	—	1 (2)	—	—	—
Alopecia	3 (5)	—	—	—	—
Respiratory					
Dyspnea	9 (14)	—	—	—	—
Cough	6 (10)	—	—	—	—
Worsening of COPD	—	—	—	1 (4)	—
Gastrointestinal					
Diarrhea	6 (10)	—	—	—	—
Dysgeusia	4 (6)	—	—	—	—
Other					
Sudden death of unknown cause	—	—	1 (2)	—	—
ALT/AST/GGT increase	9 (14)	4 (6)	—	1 (4)	2 (9)
Tumor lysis syndrome	—	3 (5)	—	—	—
Fever of unknown origin	8 (13)	2 (3)	—	—	—
Creatinine increase	9 (14)	1 (2)	—	1 (4)	1 (4)
Asthenia/fatigue	12 (19)	—	—	—	—
Sleeping disorders	12 (19)	—	—	5 (22)	—
Headache	6 (10)	—	—	2 (9)	—
Hyperglycemia	4 (6)	1 (2)	—	2 (9)	—
Cushing syndrome	4 (6)	—	—	4 (17)	—
Appetite loss	4 (6)	—	—	—	—
Cataract	—	—	—	1 (4)	1 (4)

Abbreviations: ALT, serum alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; GGT, γ-glutamyl transferase; SAE: serious adverse event.
[a]One SAE was a dose-limiting toxicity (DLT).
[b]Two SAEs were DLTs.

MM established the superiority of bendamustine to melphalan,[7] and bendamustine-bortezomib combinations were efficacious and well tolerated in this setting, including patients who had renal impairment.[14,20] However, because many patients already had received bortezomib during front-line therapy,[11,13] increased PN was an issue. With effective supportive therapy available,[21,22] a reasonable quality of life is achievable even in patients with

advanced MM. Therefore, outpatient therapy with little additional sequelae should be the goal.

When studied with carfilzomib, bendamustine was set at a fixed dose of 70 mg/m^2, which was in the range previously identified as efficient in other combination therapies for MM.[11,13,23] The schedule with application on days 1 and 8 of a cycle provides increased individual flexibility and, at this dose level, may add to excellent gastrointestinal tolerability. Several carfilzomib doses and schedules have been tested and administered.[2,14,24-26] However, in combination therapies, the optimal carfilzomib dose depends on the partner drug. In combination with bendamustine in the patient population with advanced disease treated here, the hematologic toxicities and infections observed when the carfilzomib dose was stepped up to 36 mg/m^2 led to retention of the initial dose of 27 mg/m^2 twice weekly for the subsequent phase 2 portion of the study. This choice is supported by the impressive responses already observed at this dose level used in other carfilzomib combinations in the relapse setting.[14] When administered with dexamethasone as a doublet regimen, carfilzomib at a dose of 70 mg/m^2 once weekly recently proved to be superior to 27 mg/m^2 twice weekly.[27] A limitation of our trial is the use of twice-weekly carfilzomib, but a convenient schedule with once-weekly application should be possible. KBd given this way in younger or less pretreated patients may allow a more intense 1-day carfilzomib dosing.

Of note, the patients receiving KBd were not only heavily pretreated, but a considerable portion (25%) also was aged >70 years. KBd did not lead to vomiting, hair loss, or, importantly, additional or severe PN. Because toxicities remaining from a prior regimen are a significant selection factor for subsequent therapy,[28] this combination can be applied in the large group of patients with prior PN. Remarkably, renal toxicity was not observed in this study, although patients with moderate renal impairment could participate. Although not formally tested here, renal impairment should not be a restriction.[29-31] Cardiac events and hypertension are known to be associated with carfilzomib and dexamethasone.[32,33] In our study, 4 of 6 patients with cardiac events/hypertension had prior cardiac events/hypertension, and 2 of 6 patients had prior thrombosis. Clearly, this side-effect spectrum requires attention, the use of antithrombotic prophylaxis may be considered, and the risk/benefit must be carefully evaluated in patients who have a medical history of cardiovascular events.[32,33] Both bendamustine and carfilzomib may lead to severe lymphopenia in these already immunocompromised patients. This is why, in addition to herpes virus prophylaxis, prophylactic antibiotics such as cotrimoxazole were mandatory. Immunoglobulin substitutions would be advisable in patients with secondary immunodeficiency.

In the EMN09 study, KBd was received >5 years after initial diagnosis by almost one-half of the patient population beyond the third line of treatment. The observed ≥VGPR rate was remarkable. Responses were also rapid, which is of benefit in these relapsing patients. The depth of responses and the PFS of 11.6 months with KBd at this disease stage compares favorably with other regimens, including bortezomib-containing combinations[12,13,34] and also some carfilzomib-containing[35-37] and/or pomalidomide-containing[38,39] 3-drug regimens. Even better results may be achievable with CD38 monoclonal antibodies added to carfilzomib earlier in the disease course. Although KBd may also allow combination with antibodies, it has to be acknowledged that at least CD38 antibody combinations will be soon less appealing with more frequent use of antibodies with this specificity upfront.[40-42] The use of chemotherapeutic agents, such as cyclophosphamide or bendamustine, in RRMM is supported by studies in combination with IMiDs and PIs.[23,43-45] Combinations that include carfilzomib plus chemotherapy may be options at the time of relapse, provided that these agents were not received before. At the time of relapse, the KBd combination may be an active, outpatient treatment option for many patients who have RRMM with little limitations because of comorbidities other than cardiovascular impairment. The combination partner bendamustine is well tolerated and effective at the dose applied here.[7,46] Since it has become generic, in many countries, the KBd combination may come at a competitive price, offering a reasonable alternative in the context of an incurable disease, in which multiple lines of therapy are needed—often also causing a significant financial burden.[47,48] It remains to be determined whether currently introduced treatment strategies, including immunotherapy with bispecific antibodies or chimeric antigen receptor T cells, will change this perspective.

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CONFLICTS OF INTEREST DISCLOSURES

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the advisory boards of Amgen, Celgene, Janssen Pharmaceuticals, Takeda, BMS, Roche, AbbVie, Adaptive, and Seattle Genetics outside the submitted work. Andreas Günther reports honoraria from Amgen, Celgene, Janssen Pharmaceuticals, Takeda, and Jazz Pharmaceutics; and service on the advisory boards of Amgen, Celgene, Janssen Pharmaceuticals, Takeda, Roche, Novartis, and AbbVie outside the submitted work. Massimo Offidani reports honoraria from Amgen, BMS, Celgene, Janssen Pharmaceuticals, and Takeda; and service on the advisory boards of Amgen, BMS, Celgene, Janssen Pharmaceuticals, and Takeda outside the submitted work. Monika Engelhardt reports educational grants from Janssen Pharmaceuticals, Takeda, Celgene, BMS, and Amgen outside the submitted work. Vittorio Montefusco reports travel grants from Amgen and service on the Amgen advisory board outside the submitted work. Francesca Patriarca reports service on the advisory boards of Celgene and Janssen Pharmaceuticals. Sara Aquino reports service on the advisory board of Celgene, Amgen, and Janssen Pharmaceuticals outside the submitted work. Wolfram Pönisch reports consultancy fees from Sanofi, Pfizer, Gilead Novartis, Celgene, Amgen, and Takeda; and educational grants from Gilead, Celgene, Jazz Pharmaceutics, Sanofi, and Amgen outside the submitted work. Paolo Corradini reports service on the advisory boards of AbbVie, Amgen, Celgene, Daiichi Sankyo, Gilead, Incyte, Janssen Pharmaceuticals, Kite, Kiowa, Kirin, Novartis, Roche, Sanofi, Servier, and Takeda; and honoraria from AbbVie, Amgen, Celgene, Janssen Pharmaceuticals, Jazz Pharmaceutics, Novartis, Roche, Sanofi, Sandoz, and Takeda outside the submitted work. Herman Einsele reports research support from Janssen Pharmaceuticals, Celgene, Amgen, and BMS; service on the speaker's bureaus or advisory boards of Janssen Pharmaceuticals, Celgene, Amgen, BMS, Novartis, and Takeda; and honoraria from Janssen Pharmaceuticals, Celgene, Amgen, BMS, Novartis, and Takeda outside the submitted work. Mario Boccadoro reports honoraria from Sanofi, Celgene, Amgen, Janssen Pharmaceuticals, Novartis, BMS, and AbbVie; and research funding from Sanofi, Celgene, Amgen, Janssen Pharmaceuticals, Novartis, BMS, and Mundipharma outside the submitted work. Antonio Palumbo is an employee of GlaxoSmithKline. Pieter Sonneveld reports research funding from Amgen, Celgene, Janssen Pharmaceuticals, Karyopharm, SkylineDx, and Takeda; and honoraria from Amgen, BMS, Celgene, Janssen Pharmaceuticals, Karyopharm, and Takeda outside the submitted work. Martin Gramatzki reports service on the advisory boards of Amgen, BMS, Celgene, Novartis, Oncopeptides, and Takeda outside the submitted work. The remaining authors made no disclosures

AUTHOR CONTRIBUTIONS

Francesca Gay: Designed and performed the research study, analyzed the data, and wrote the article. **Stefano Spada:** Analyzed the data. **Martin Gramatzki:** Designed and performed the research study, analyzed the data, and wrote the article. All authors contributed patients or study material and reviewed and approved the final version for submission.

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